Submission of Clinical and Economic Data Supporting Formulary Consideration of LUVOX® CR

(fluvoxamine maleate) Extended-Release Capsules

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EXECUTIVE SUMMARY

LUVOX® CR is a once-daily formulation of fluvoxamine maleate, a selective serotonin reuptake inhibitor (SSRI) that is indicated for the treatment of obsessive compulsive disorder (OCD) and social anxiety disorder (SAD).[1] LUVOX® CR is available in 100 mg and 150 mg strengths for daily dosing ranging from 100-300 mg.

OBSESSIVE COMPULSIVE DISORDER

OCD is an anxiety disorder characterized by obsessive, distressing, intrusive thoughts (obsessions) and/or compulsions (tasks or rituals).[2]

OCD is a rare disorder, affecting approximately 1.6% of Americans.[3] The disorder usually begins in early adulthood[4] and has a chronic and fluctuating course.[5, 6]

OCD causes significant patient and family burden. The World Health Organization ranks OCD among the top ten most disabling medical and psychiatric conditions, accounting for 2.2% of disability worldwide.[7]

Patient Burden:

- One quarter (25.7%) of individuals meeting criteria for OCD reported having previously attempted suicide.[8]
- Among individuals with OCD, rates of prior suicide attempts:
  - Did not significantly differ in patients with pure OCD compared to patients with OCD comorbid with ICD-10 neurotic disorders;
  - Were nearly twice those reported by individuals with other ICD-10 neurotic disorders (25.7% versus 14.5%, p=0.005);[8] and
  - Were over 11 times greater than those reported by individuals without ICD-10 neurotic disorders (25.7% versus 2.3%, p<0.001).[8]
- The functional status of patients with severe OCD is comparable to that of patients with schizophrenia.[9]
- One-third of individuals with OCD are unable to work due to their illness.[10]
- Persons with OCD lose, on average, 3 years of wages during their lifetimes due to the disorder.[11]

Family Burden:

- Relatives of patients with OCD are more depressed than relatives of patients with depression.[12]
- The families of patients with OCD often accommodate to patients' aberrant behaviors and disrupt their normal routine by, for example, submitting to "decontamination" rituals, avoiding going places or doing things that make the patient anxious, and reassuring the patient.[13-15]
- 82% of family members of those with OCD reported disruptions in personal and social activities as a result of OCD, and 60% reported marital discord, loss of leisure, and financial problems as a result of the disorder.[13]

Under-detection:

- Research suggests that OCD remains an under-detected disorder. Physician lack of training and time regarding screening for OCD and patient embarrassment about their symptoms are factors that may contribute to this problem.[16, 17]
- In a Health Maintenance Organization (HMO) population, only 0.084% of patients were diagnosed with OCD,[18] a rate less than one tenth that of the general population prevalence estimate of OCD. Researchers concluded that these findings suggest substantial under-detection of this disorder.[18]

- Although one study found that the majority of patients with OCD (64%) reported having discussed emotional problems with their doctor, in another study, only 1 in 3 persons with OCD reported having specifically disclosed their OCD symptoms to their doctor.[19]
- Patients with OCD report a lag of:
  - 10 to 11 years between onset of their OCD and seeking professional help[11] or receiving treatment for OCD;[20] and
  - 6 years between seeking professional help and receiving a correct diagnosis.[11]

Healthcare System Burden:
The burden of OCD currently borne by the healthcare system is substantial.

- Patients with OCD are three times as likely as individuals with other neuroses to have ever been admitted to an inpatient mental health facility (20% versus 6%, $p<0.001$).[16]
- The portal of care for OCD is much more likely to occur within the medical rather than the mental health setting.[21]
- Compared with individuals without psychiatric diagnoses, those with OCD have 63% higher mean costs for nonpsychiatric visits and 56% higher costs for laboratory/radiology services.[22]
- Patients with OCD frequently have contamination or illness concerns; these may drive patients to seek medical (rather than psychiatric) care.[2]
- One study found that while patients with OCD were no more likely than a comparison group of graduate students to receive primary care services in the past year, they were almost twice as likely to have consulted with a specialist.[23]
- Washing rituals or compulsive skin picking may lead to skin problems.[23-25]
- Patients with OCD often present at dermatology clinics.
  - Studies of patients in dermatology clinics report that 14% to 25% satisfy criteria for current OCD.[24-26]
  - In these studies, most patients (85% and 94%) meeting diagnostic criteria for OCD had not been previously identified with OCD.[24, 25]
- In a matched comparison of Florida Medicaid adult patients with pure OCD (OCD without comorbid depression, bipolar disorder, or psychoses) and patients with pure depression (depression without comorbid OCD, bipolar disorder, or psychoses), those with pure OCD had an approximately 2 times greater 2-year, median, per-patient total (inpatient, outpatient, and pharmacy) number of healthcare claims (126.0 versus 68.4, $p<0.0001$) and 3 times higher total costs ($25,666 versus $7,732, $p<0.0001$) than those with pure depression.[27] Much of the difference in healthcare utilization between these groups was accounted for by a 65% greater median number of outpatient visits for medical treatment among those with pure OCD versus pure depression (86.0 versus 56.0, $p=0.0007$), which resulted in an approximately 2 times greater median medical cost for outpatient visits for those with pure OCD than for their counterparts with pure depression.

Inappropriate and/or Inadequate Treatment:
Once detected, OCD is frequently inappropriately and/or inadequately treated.

- In a study of HMO patients newly diagnosed with OCD, more than half (57.2%) received either no medication (27.5%) or an inadequate dose and/or duration of pharmacotherapy (29.7%).[28]
- In a retrospective analysis over 9 years (1997-2006) of Florida Medicaid-enrolled adults newly diagnosed with OCD who received SSRIs (n=987), investigators examined adequacy of treatment defined as adequate duration of treatment (at least 12 consecutive weeks) and adequate dose of treatment during the maintenance phase of therapy (according to minimum guideline-recommended minimally effective dose ranges during treatment maintenance).[29]

  - In total, 75% received inadequate pharmacotherapy (both inadequate duration and dose) during the study period.
    - 23% of patients received less than 12 weeks on an SSRI, and
    - 77% received SSRI doses below the minimum guideline-recommended target range.
- A survey of U.S. psychiatrists who treated 123 patients with OCD from 1997 to 1999 revealed that, although 65% of patients with OCD received appropriate medication (serotonin reuptake inhibitors; SRIs), only 39.4% of patients received doses at an effective therapeutic level.[30]
- Similarly, in interviews conducted with patients with OCD upon admission to an outpatient clinic, approximately 50% of patients were prescribed appropriate medications, but many patients received doses below therapeutic levels.[31]

The Cost of Under-detection and Inappropriate and/or Inadequate Treatment:
Under-detection and inappropriate or inadequate treatment of OCD are unfortunate given the high cost of the disorder.

- Results of a 1995 survey of patients with OCD found that 6-month outpatient provider fees were significantly higher among those who received inappropriate (defined as incorrect diagnosis or no SRI) versus appropriate pharmacotherapy.[11]
  - Specifically, the 6-month costs for provider fees among those receiving inappropriate pharmacotherapy were $2,811 versus $1,958 (p=0.05) for those receiving appropriate pharmacotherapy (both in 2007 values).
  - The total (direct and indirect) annual cost of inappropriate treatment for all individuals with OCD was estimated at $2.4 billion in 1995 ($3.8 billion in 2007 values).

SOCIAL ANXIETY DISORDER

SAD is characterized as a pervasive fear of social situations and evaluation by others,[2] and occurs in approximately 6.8% of the U.S. population.[3] The disorder usually begins during middle adolescence[32] and follows a chronic course.[2]

Patient Distress and Decrements in Quality of Life:
SAD is associated with substantial patient distress and decrements in quality of life.

- Individuals with SAD are 6 times more likely to have made a suicide attempt than those without psychiatric disorders.[33]
- Compared to 5% of controls who suffer from chronic infection of a sexually transmitted disease, more than 50% of persons with SAD report a markedly reduced quality of life.[34]

Under-detection:
Although persons with SAD may frequently come into contact with primary care providers (PCPs), SAD remains under-detected.

- In a managed care population, only 0.5% of patients meeting diagnostic criteria for SAD were correctly diagnosed.[35]
- PCPs fail to diagnose 3 of every 4 patients who meet diagnostic criteria for SAD.[36]
- Compared to patients with other anxiety disorders, those with SAD are significantly less likely to be correctly diagnosed by their PCPs.[37]

Healthcare System Burden:
Much of the burden of SAD is borne by the healthcare system.

- Compared to those without any psychiatric disorder, individuals with SAD:
  - Visit medical providers more than 2 times as frequently,[38] and
  - Have 8 times more outpatient visits[39] and 9 times more mental health visits.[38]

- Outpatient costs are 1.3 and 1.5 times higher among patients with pure and comorbid SAD (respectively) than among those without any psychiatric disorders.[35]

Based on the research presented in this dossier, the value that LUVOX® CR can bring to a healthcare plan is summarized as follows:

- LUVOX® CR, a once-daily capsule, is specifically formulated to deliver:
  - Less peak and trough fluctuation in plasma levels compared to the IR formulation
  - Lower and later peak plasma concentrations of fluvoxamine
  - Higher trough concentrations of fluvoxamine.

- Reduced fluctuations in plasma concentration may be associated with a lower incidence of peak-related adverse events; a lower peak concentration may allow patients to initiate treatment at a higher dose without increasing the risk of peak-related adverse events.

Clinical Trial Results:

- Compared to placebo
  - LUVOX® CR demonstrates a statistically significant reduction in OCD symptoms (as measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) at week 12.
    - A statistically significant effect occurred as early as week 2.
    - Sustained improvement occurred through week 12.
  - LUVOX® CR is associated with significantly reduced SAD symptoms (as measured by the Liebowitz Social Anxiety Scale (LSAS) at week 12.
    - A statistically significant effect occurred as early as week 4 although it was not sustained at week 6 in one study.
    - Sustained improvement occurred through week 12.
  - Patients treated with LUVOX® CR demonstrate significant benefits with regard to disease severity and functioning.
  - LUVOX® CR is well tolerated.
  - Many of the most frequently experienced side effects are mild to moderate in nature and transient.
  - Evidence indicates that LUVOX® CR does not result in significant weight gain or loss.
  - No significant difference in sexual dysfunction, as defined by the Arizona Sexual Experiences (ASEX) scale, was seen in patients receiving LUVOX® CR versus placebo in two SAD clinical trials.

VALUE TO THE PAYER

LUVOX® CR is indicated for the treatment of OCD, a rare but severely disabling disorder, and SAD, a more common but also substantially impairing condition. Although both of these disorders have a profound effect on individuals' ability to function in occupational and social settings, they are frequently under-detected by patients' physicians or are inappropriately treated. These disorders place a high burden on patients' families, healthcare systems, and society in general.

Treatment for appropriately diagnosed patients with OCD or SAD includes psychotherapy and pharmacotherapy. For OCD, first-line, U.S. Food and Drug Administration (FDA)-approved pharmacological treatments include the SSRIs fluoxetine, fluvoxamine (IR and CR), paroxetine (IR and CR), and sertraline, and the SRI clomipramine. For SAD, first-line, FDA-approved pharmacological treatments include the SSRIs fluoxetine, fluvoxamine (CR), paroxetine (IR and CR), and sertraline, and the selective norepinephrine reuptake inhibitor (SNRI) venlafaxine (XR).

The recent addition of LUVOX® CR to the armamentarium of treatment options for OCD and SAD offers patients and physicians a once-daily medication with the ability to achieve clinically meaningful

reductions in symptoms at 12 weeks and statistical separation as early as 2 and 4 weeks for OCD and SAD, respectively. In addition, LUVOX® CR is well tolerated, possesses a weight neutral profile (no significant weight gain or loss), and has a low incidence of sexual side effects. The drug delivery technology utilized by LUVOX® CR, SODAS® (Spheroidal Oral Drug Absorption System), is specifically formulated to deliver:

- Less peak and trough fluctuation in plasma levels compared to the IR formulation
- Lower and later peak plasma concentrations of fluvoxamine
- Higher trough concentrations of fluvoxamine

Reduced fluctuations in plasma concentration may be associated with a lower incidence of peak-related adverse events; a lower peak concentration may allow patients to initiate treatment at a higher dose without increasing the risk of peak-related adverse events.

In sum, patients with OCD and SAD often suffer silently with devastating symptoms for many years before receiving help. Because there are now a number of effective pharmacological treatments for these disorders, physicians may work with patients to determine the medication that best suits the needs of the individual, and take into consideration issues of time to effect, tolerability, and convenience. LUVOX® CR should be considered, along with other FDA-approved treatments, for these conditions.

PRODUCT INFORMATION

AHFS CLASSIFICATION

28:16.04.20 Selective Serotonin Reuptake Inhibitors

LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules
100 mg and 150 mg

Rx Only

Suicidality and Antidepressant Drugs

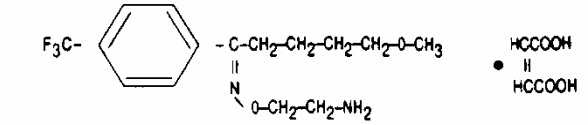
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. LUVOX CR Capsules are not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION

LUVOX® CR is an extended-release capsule for oral administration that contains fluvoxamine maleate, a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to the distinct chemical series, the 2-aminoethyl oxime ethers of aralkylketones.

Fluvoxamine maleate is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4′-(trifluoromethyl) valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3 \bullet C_4H_4O_4$. Its molecular weight is 434.41.

The structural formula is:



Fluvoxamine maleate is a white to off-white, odorless, crystalline powder that is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

LUVOX® CR Capsules are available in 100 mg and 150 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each capsule contains the following inactive ingredients: talc, sugar spheres, ammonio methacrylate copolymer type B, dibutyl sebacate, red iron oxide, FD&C Blue No. 2, titanium dioxide, gelatin (porcine- or bovine-derived), and Opacode Grey. LUVOX® CR Capsules are gluten-free.

How Supplied

Dosage Forms of LUVOX® CR

Dose	Package Size	Color	NDC #	WAC ($)
100 mg Extended-Release Capsule	Bottle of 30 Capsules	dark blue opaque cap/white opaque body	68727-600-01	$97.50
150 mg Extended-Release Capsule	Bottle of 30 Capsules	dark blue opaque cap/powder blue opaque body	68727-601-01	$97.50

Storage

LUVOX® CR Capsules should be protected from high humidity and stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Avoid exposure to temperatures above 30°C (86°F).

Dispense in tight containers.

Keep out of reach of children.

INDICATIONS AND USAGE

Social Anxiety Disorder

LUVOX® CR Capsules are indicated for the treatment of social anxiety disorder (SAD), also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of LUVOX® CR Capsules was demonstrated in two 12-week trials in adult patients with social anxiety disorder (DSM-IV). LUVOX® CR Capsules have not been studied in children or adolescents with social anxiety disorder (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**).

The effectiveness of LUVOX® CR Capsules in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the health care provider who elects to prescribe LUVOX® CR Capsules for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Obsessive Compulsive Disorder

LUVOX® CR Capsules are indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD), as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of LUVOX® CR Capsules was demonstrated in one 12-week trial with obsessive compulsive outpatients with the diagnosis of OCD as defined in DSM-IV (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**).

The efficacy of the immediate-release fluvoxamine maleate tablets in the treatment of OCD was demonstrated in two 10-week multicenter, parallel-group studies of adult outpatients.

Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of LUVOX® CR Capsules for long-term use, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the health care provider who elects to prescribe LUVOX® CR Capsules for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of fluvoxamine maleate in obsessive compulsive disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. Fluvoxamine has been shown to be a potent inhibitor of the serotonin reuptake transporter in preclinical studies, both *in vitro* and *in vivo*.

In *in vitro* studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is thought to be associated with various sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotropic drugs.

Pharmacokinetics

Bioavailability*:* A single-dose crossover study in 28 healthy subjects was conducted to compare the pharmacokinetics of fluvoxamine after administration of LUVOX® CR Capsules and immediate-release fluvoxamine maleate tablets.

In the single-dose crossover study, mean C_{max} was 38% lower and relative bioavailability was 84% for LUVOX® CR Capsules versus immediate-release fluvoxamine maleate tablets.

In a multiple-dose proportionality study, LUVOX® CR Capsules were administered over a dose range of 100 mg/day to 300 mg/day to 20 healthy volunteers. Steady-state plasma concentrations were achieved within a week of dosing. Mean maximum plasma concentrations were 47 ng/mL, 161 ng/mL, and 319 ng/mL, respectively, at the 100 mg, 200 mg, and 300 mg administered dose levels. Fluvoxamine exhibited nonlinear pharmacokinetics producing disproportionately higher concentrations over the dose range. The AUC and C_{max} values increased 5.7-fold following the 3-fold increase in dose from 100 mg to 300 mg.

Food caused the mean AUC and C_{max} of fluvoxamine to increase only slightly; therefore, administration of LUVOX CR Capsules with food does not significantly affect the absorption of fluvoxamine.

Distribution/Protein Binding: The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution.

Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 ng/mL to 2000 ng/mL.

Metabolism: Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the

parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (see **PRECAUTIONS – Drug Interactions.**)

Elimination: Following a ^{14}C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours.

After administration of a 100 mg, single oral dose of LUVOX® CR Capsules, the mean plasma half-life of fluvoxamine in healthy male and female volunteers was 16.3 hours.

Gender: In a study with 15 male and 13 female healthy volunteers who were administered LUVOX® CR Capsules 100 mg, AUC and C_{max} of fluvoxamine were increased by approximately 60% in females compared to males. There were no differences in the elimination half-life between males and females.

Elderly Subjects: In a study using immediate-release fluvoxamine maleate tablets at 50 mg and 100 mg and comparing elderly (ages 66-73 years) and young subjects (ages 19-35 years), mean maximum plasma concentrations in the elderly were 40% higher. The multiple-dose elimination half-life of fluvoxamine was 17.4 hours and 25.9 hours in the elderly compared to 13.6 hours and 15.6 hours in the young subjects at steady state for 50 mg and 100 mg doses, respectively.

In elderly patients administered immediate-release fluvoxamine maleate tablets, the clearance of fluvoxamine was reduced by about 50%; therefore, LUVOX® CR Capsules should be slowly titrated during initiation of therapy.

Pediatric Subjects*:* The pharmacokinetics of LUVOX® CR Capsules have not been evaluated in pediatric patients. However, the multiple-dose pharmacokinetics of immediate-release fluvoxamine maleate tablets were determined in male and female children (ages 6-11 years) (Table 2) and adolescents (ages 12-17 years) (Table 1). Steady-state plasma fluvoxamine concentrations were 2-fold to 3-fold higher in children than in adolescents. AUC and C_{max} in children were 1.5-fold to 2.7-fold higher than those in adolescents (See Table 1). As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and C_{max} compared to male children; therefore, lower doses of immediate-release fluvoxamine maleate tablets may produce therapeutic benefit (See Table 2). No gender differences were observed in adolescents. Steady-state plasma fluvoxamine concentrations were similar in adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in these two populations (See Table 1). Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

TABLE 1. COMPARISON OF MEAN (SD) IMMEDIATE-RELEASE TABLET FLUVOXAMINE MALEATE PHARMACOKINETIC PARAMETERS BETWEEN CHILDREN, ADOLESCENTS, AND ADULTS

PHARMACOKINETIC PARAMETER (BODY WEIGHT CORRECTED)	DOSE =200 MG/DAY (100 MG TWICE DAILY)		DOSE =300 MG/DAY (150 MG TWICE DAILY)	
	CHILDREN (N=10)	ADOLESCENT (N=17)	ADOLESCENT (N=13)	ADULT (N=16)
AUC 0-12 (ng•h/mL/kg)	155.1 (160.9)	43.9 (27.9)	69.6 (46.6)	59.4 (40.9)
C_{max} (ng/mL/kg)	14.8 (14.9)	4.2 (2.6)	6.7 (4.2)	5.7 (3.9)
C_{min} (ng/mL/kg)	11.0 (11.9)	2.9 (2.0)	4.8 (3.8)	4.6 (3.2)

TABLE 2. COMPARISON OF MEAN (SD) IMMEDIATE-RELEASE TABLET FLUVOXAMINE MALEATE PHARMACOKINETIC PARAMETERS BETWEEN MALE AND FEMALE CHILDREN (6-11 YEARS)

PHARMACOKINETIC PARAMETER (BODY WEIGHT CORRECTED)	DOSE =200 MG/DAY (100 MG TWICE DAILY)	
	MALE CHILDREN (N=7)	FEMALE CHILDREN (N=3)
AUC 0-12 (ng•h/mL/kg)	95.8 (83.9)	293.5 (233.0)
C_{max} (ng/mL/kg)	9.1 (7.6)	28.1 (21.1)
C_{min} (ng/mL/kg)	6.6 (6.1)	21.2 (17.6)

***Hepatic and Renal Disease**:* A cross-study comparison (healthy subjects versus patients with hepatic dysfunction) using immediate-release fluvoxamine maleate tablets suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 mL/min to 45 mL/min) after 4 weeks and 6 weeks of treatment (50 mg given twice daily, N=13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients (see **PRECAUTIONS – *Use in Patients with Concomitant Illness*)**.

CLINICAL TRIALS

Social Anxiety Disorder

The effectiveness of LUVOX® CR Capsules in the treatment of social anxiety disorder was demonstrated in two 12-week, multicenter, placebo-controlled studies of adult outpatients with social anxiety disorder (DSM-IV). Patients in these trials were titrated in 50 mg increments over the first six weeks of the study on the basis of response and tolerance from a dose of 100 mg/day to a fluvoxamine maleate dose within a range of 100 mg to 300 mg once-a-day.

In these studies, the effectiveness of LUVOX® CR Capsules compared to placebo was evaluated on the basis of change from baseline in the Liebowitz Social Anxiety Scale (LSAS). LUVOX® CR Capsules demonstrated a statistically significant superiority over placebo at the primary endpoint (Week 12) as assessed by the LSAS total score in both studies.

The mean daily doses of LUVOX® CR Capsules administered to patients in Study 1 and Study 2 were 236 mg and 204 mg, respectively, at end of study.

Subgroup analyses generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

Obsessive Compulsive Disorder (OCD)

The effectiveness of LUVOX® CR Capsules for the treatment of OCD was demonstrated in a 12-week, multicenter, placebo-controlled study of adult outpatients. Patients in this trial were titrated in 50 mg increments over the first six weeks of the study on the basis of response and tolerance from a dose of 100 mg/day to a fluvoxamine maleate dose within a range of 100 mg to 300 mg once-a-day. Patients in this study had moderate to severe OCD (DSM-IV), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total scores of 26.6 and 26.3 for fluvoxamine and placebo-treatment groups, respectively.

Patients receiving LUVOX® CR Capsules demonstrated statistically significant improvement over placebo patients at the primary endpoint (Week 12) compared to baseline on the Y-BOCS. The mean daily dose of LUVOX® CR Capsules administered to patients was 261 mg at end of study.

Exploratory analyses for age and gender effects on outcomes did not show any significant differential responsiveness on the basis of age or sex.

The effectiveness of immediate-release fluvoxamine maleate tablets for the treatment of OCD was demonstrated in two 10-week multicenter, parallel-group studies of adult outpatients. Patients in these trials were titrated to a total daily fluvoxamine maleate dose of 150 mg/day over the first two weeks of the trial, after which the dose was adjusted within a range of 100 mg/day to 300 mg/day (given in two doses per day), on the basis of response and tolerance. Patients in these studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score of 23.

Pediatric OCD Study*:* LUVOX® CR Capsules have not been evaluated in pediatric patients. However, the effectiveness of immediate-release fluvoxamine maleate tablets for the treatment of OCD was demonstrated in a 10-week multicenter, parallel-group study in a pediatric outpatient population (children and adolescents, ages 8-17 years). Patients in this study were titrated to a total daily fluvoxamine dose of approximately 100 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 50 mg/day to 200 mg/day (given in two doses per day) on the basis of response and tolerance. All patients had moderate-to-severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score of 24.

Post hoc exploratory analyses for gender effects on outcomes did not suggest any differential responsiveness on the basis of gender. Further exploratory analyses revealed a prominent treatment effect in the 8 year to 11 year age group and essentially no effect in the 12 year to 17 year age group. While the significance of these results is not clear, the 2-3 fold higher steady-state plasma fluvoxamine concentrations in children compared to adolescents (see **Pharmacokinetics**) is suggestive that decreased exposure in adolescents may have been a factor, and dose adjustment in adolescents (up to the adult maximum dose of 300 mg/day) may be indicated to achieve therapeutic benefit.

CONTRAINDICATIONS

Co-administration of alosetron, tizanidine, thioridazine, or pimozide with LUVOX® CR Capsules is contraindicated (see **WARNINGS** and **PRECAUTIONS**).

The use of MAO inhibitors used in combination with LUVOX CR Capsules, or within 14 days of discontinuing treatment with LUVOX® CR Capsules, is contraindicated (see **WARNINGS** and **PRECAUTIONS**).

LUVOX® CR Capsules are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate or any of the excipients.

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. The pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults

with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in the Table 3.

TABLE 3. DRUG-PLACEBO DIFFERENCES IN NUMBER OF CASES OF SUICIDALITY PER 1000 PATIENTS TREATED

AGE RANGE	DRUG-RELATED INCREASES
<18	14 additional cases
18-24	5 additional cases
AGE RANGE	**DRUG- RELATED DECREASES**
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about the drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION — Discontinuation of Treatment with LUVOX® CR Capsules**, for a description of the risks of discontinuation of LUVOX® CR Capsules).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for LUVOX® CR Capsules should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an

episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that LUVOX® CR Capsules is not approved for use in treating bipolar depression.

Potential for Monoamine Oxidase Inhibitors Interaction

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOIs), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have discontinued that drug and have been started on an MAOI. Some cases presented with features resembling a serotonin syndrome or neuroleptic malignant syndrome. Therefore, LUVOX® CR Capsules should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI (see CONTRAINDICATIONS).

Potential Thioridazine Interaction

The effect of fluvoxamine (25 mg immediate-release tablets given twice daily for one week) on thioridazine steady-state concentrations was evaluated in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased 3-fold following co-administration of fluvoxamine.

Thioridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. It is likely that this experience underestimates the degree of risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine may be even more pronounced when it is administered at higher doses.

Therefore, LUVOX® CR Capsules and thioridazine should not be co-administered (see CONTRAINDICATIONS and PRECAUTIONS).

Potential Tizanidine Interaction

Fluvoxamine is a potent inhibitor of CYP1A2 and tizanidine is a CYP1A2 substrate. The effect of immediate–release fluvoxamine maleate tablets (100 mg daily for four days) on the pharmacokinetics and pharmacodynamics of a single dose of tizanidine has been studied in 10 healthy male subjects. Tizanidine C_{max} was increased approximately 12-fold (range 5-fold to 32-fold), elimination half-life was increased by almost 3-fold, and AUC increased 33-fold (range 14-fold to 103-fold). The mean maximal effect on blood pressure was a 35 mm Hg decrease in systolic blood pressure, a 20 mm Hg decrease in diastolic blood pressure, and a 4 beat/min decrease in heart rate. Drowsiness was significantly increased and performance on the psychomotor task was significantly impaired. LUVOX CR Capsules and tizanidine should not be used together (see CONTRAINDICATIONS and PRECAUTIONS).

Potential Alosetron Interaction

Fluvoxamine, an inhibitor of several CYP isozymes, has been shown to increase mean alosetron plasma concentrations (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. Consequently, it is recommended that LUVOX® CR Capsules not be used in combination with alosetron (see CONTRAINDICATIONS, PRECAUTIONS, and Lotronex™ (alosetron) package insert).

Use with Ramelteon

Ramelteon should not be used in combination with LUVOX® CR Capsules (see **PRECAUTIONS: Drug Interactions**).

Potential Pimozide Interaction

Pimozide is metabolized by the CYP3A4 isozyme, and it has been demonstrated that ketoconazole, a potent inhibitor of CYP3A4, blocks the metabolism of this drug, resulting in increased plasma concentrations of parent drug. Increased plasma concentration of pimozide causes QT prolongation and has been associated with torsades de pointes-type ventricular tachycardia, sometimes fatal. As noted below, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is known to be metabolized by the CYP3A4 isozyme. Although it has not been definitively demonstrated that fluvoxamine is a potent CYP3A4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with pimozide (see CONTRAINDICATIONS and PRECAUTIONS).

Other Potentially Important Drug Interactions

(Also see **PRECAUTIONS – Drug Interactions.**)

Benzodiazepines*:* Benzodiazepines metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be reduced by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.

Alprazolam – When immediate-release fluvoxamine maleate tablets (100 mg given once daily) and alprazolam (1 mg given 4 times per day) were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, $T_{½}$) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100 mg to 300 mg. If alprazolam is co-administered with LUVOX CR Capsules, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for LUVOX® CR Capsules.

Diazepam – The co-administration of LUVOX® CR Capsules and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, N-desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species during chronic co-administration.

Evidence supporting the conclusion that it is inadvisable to co-administer fluvoxamine and diazepam is derived from a study in which healthy volunteers taking 150 mg/day of immediate-release fluvoxamine maleate tablets were administered a single oral dose of 10 mg of diazepam. In these subjects (N=8), the clearance of diazepam was reduced by 65% and that of N-desmethyldiazepam to a level that was too low to measure over the course of the two-week long study.

It is likely that this experience significantly underestimates the degree of accumulation that might occur with repeated diazepam administration. Moreover, as noted with alprazolam, the effect of fluvoxamine may even be more pronounced when it is administered at higher doses.

Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered.

Mexiletine – The effect of steady-state immediate-release fluvoxamine maleate tablets (50 mg given twice daily for 7 days) on the single-dose pharmacokinetics of mexiletine (200 mg) was evaluated in 6 healthy Japanese males. The clearance of mexiletine was reduced by 38% following co-administration

with fluvoxamine compared to mexiletine alone. If fluvoxamine and mexiletine are co-administered, serum mexiletine levels should be monitored.

Neuroleptic Malignant Syndrome (NMS) or NMS-Like Events*:* Rare instances of neuroleptic malignant syndrome (NMS) or NMS-like events have been reported in association with fluvoxamine treatment when co-administered with anti-psychotics. Additionally, a small number of such cases have been reported with fluvoxamine treatment in the absence of anti-psychotic co-administration. These serious and sometimes fatal events can include hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes. As these events may result in potentially life-threatening conditions, patients receiving this combination of therapy should be monitored for the emergence of NMS-like signs and symptoms. Treatment with fluvoxamine and any concomitant anti-psychotic agent should be discontinued immediately if such events occur and supportive symptomatic treatment should be initiated.

Theophylline*:* The effect of steady-state immediate-release fluvoxamine maleate tablets (50 mg tablets given twice daily) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy non-smoking, male volunteers. The clearance of theophylline was decreased approximately 3-fold. Therefore, if theophylline is co-administered with fluvoxamine maleate, its dose should be reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for LUVOX® CR Capsules.

Warfarin*:* When immediate-release fluvoxamine maleate tablets (50 mg given three time per day) were administered concomitantly with warfarin for two weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX® CR Capsules should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX® CR Capsules.

Serotonin Syndrome*:* The development of a potentially life-threatening serotonin syndrome may occur with LUVOX® CR Capsules treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs that impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of LUVOX® CR Capsules with MAOIs intended to treat depression is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS – Potential for Interactions with Monoamine Oxidase Inhibitors**).

If concomitant treatment of LUVOX® CR Capsules with a 5-hydroxtryptamine receptor agonist (triptan) is clinically warranted careful observation of the patient is advised, particularly during treatment initiation and dose increase (see **PRECAUTIONS – Drug Interactions**).

The concomitant use of fluvoxamine with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS – Drug Interactions**).

PRECAUTIONS

General

Discontinuation of Treatment with LUVOX® CR Capsules: During marketing of immediate-release fluvoxamine maleate tablets and other SSRIs and SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with LUVOX® CR Capsules. A gradual reduction in dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the health care provider may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION**).

Abnormal Bleeding: SSRIs and SNRIs, including LUVOX® CR Capsules, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between the use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of LUVOX® CR Capsules and NSAIDs, aspirin, or other drugs that affect coagulation.

Activation of Mania/Hypomania: During premarketing studies of immediate-release fluvoxamine maleate tablets involving primarily depressed patients, hypomania or mania occurred in approximately 1% of patients treated with fluvoxamine. In a 10-week pediatric OCD study, 2 out of 57 patients (4%) treated with fluvoxamine experienced manic reactions, compared to none of 63 placebo patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, LUVOX® CR Capsules should be used cautiously in patients with a history of mania.

Seizures: During premarketing studies with immediate-release fluvoxamine maleate tablets, seizures were reported in 0.2% of fluvoxamine-treated patients. Caution is recommended when the drug is administered to patients with a history of convulsive disorders. Fluvoxamine should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Treatment with fluvoxamine should be discontinued if seizures occur or if seizure frequency increases.

Hyponatremia: Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including LUVOX® CR Capsules. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see **Geriatric Use**). Discontinuation of LUVOX® CR Capsules should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

Use in Patients with Concomitant Illness: Closely monitored clinical experience with immediate-release fluvoxamine maleate tablets in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX® CR Capsules to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

LUVOX® CR Capsules or immediate-release fluvoxamine maleate tablets have not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes.

In patients with liver dysfunction, following administration of immediate-release fluvoxamine maleate tablets, fluvoxamine clearance was decreased by approximately 30%. Patients with liver dysfunction should begin with a low dose of LUVOX® CR Capsules and increase it slowly with careful monitoring.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with LUVOX® CR Capsules and should counsel them in the appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for LUVOX® CR Capsules. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking LUVOX® CR Capsules.

Abnormal Bleeding: Patients should be cautioned about the concomitant use of fluvoxamine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Clinical Worsening and Suicide Risk: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate the need for very close monitoring and possibly changes in the medication.

Interference with Cognitive or Motor Performance: Since any psychoactive drug may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that LUVOX® CR Capsules therapy does not adversely affect their ability to engage in such activities.

Pregnancy: Patients should be advised to notify their health care providers if they become pregnant or intend to become pregnant during therapy with LUVOX® CR Capsules.

Nursing: Patients receiving LUVOX® CR Capsules should be advised to notify their health care providers if they are breast feeding an infant (see **PRECAUTIONS – Nursing Mothers**).

Concomitant Medication: Patients should be advised to notify their health care providers if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with LUVOX® CR Capsules. Patients should be cautioned about the concomitant use of LUVOX® CR Capsules and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of LUVOX® CR Capsules and triptans, tramadol or other serotonergic agents.

Because of the potential for the increased risk of serious adverse reactions, including severe lowering of blood pressure and sedation, when LUVOX® CR Capsules and tizanidine are used together, fluvoxamine should not be used with tizanidine.

Because of the potential for the increased risk of serious adverse reactions when LUVOX® CR Capsules and alosetron are used together, fluvoxamine should not be used with Lotronex™ (alosetron).

Alcohol: Patients should be advised to avoid alcohol while taking LUVOX® CR Capsules.

Allergic Reactions: Patients should be advised to notify their health care providers if they develop a rash, hives, or a related allergic phenomenon during therapy with LUVOX® CR Capsules.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes: Multiple hepatic cytochrome P450 isoenzymes are involved in the oxidative biotransformation of a large number of structurally different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the cytochrome P450 isoenzyme system has been obtained mostly from pharmacokinetic interaction studies conducted in healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and also **WARNINGS** for details) and limited *in vitro* data for CYP3A4, it appears that fluvoxamine inhibits several cytochrome P450 isoenzymes that are known to be involved in the metabolism of other drugs such as: CYP1A2 (e.g. warfarin, theophylline, propranolol, tizanidine), CYP2C9 (e.g. warfarin), CYP3A4 (e.g. alprazolam), and CYP2C19 (e.g. omeprazole).

In vitro data suggest that fluvoxamine is a relatively weak inhibitor of CYP2D6.

Approximately 7% of the normal population has a genetic code that leads to reduced levels of activity of CYP2D6 enzyme. Such individuals have been referred to as "poor metabolizers" (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an *in vivo* study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 "extensive metabolizers" (EM): mean C_{max}, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by CYP2D6. Caution is indicated in patients known to have reduced levels of cytochrome P450 2D6 activity and those receiving concomitant drugs known to inhibit this cytochrome P450 isoenzyme (e.g., quinidine).

The metabolism of fluvoxamine has not been fully characterized and the effects of potent cytochrome P450 isoenzyme inhibition, such as the ketoconazole inhibition of CYP3A4, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as warfarin or theophylline, certain benzodiazepines and phenytoin. If LUVOX® CR Capsules are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (see **CONTRAINDICATIONS** and **WARNINGS**).

CNS Active Drugs:

Anti-psychotics: See **WARNINGS – Other Potentially Important Drug Interactions – *Neuroleptic Malignant Syndrome (NMS) or NMS-Like Events*.**

Monoamine Oxidase Inhibitors: **See CONTRAINDICATIONS** and **WARNINGS.**

Alprazolam: See **WARNINGS.**

Diazepam: See **WARNINGS.**

Alcohol: Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other) and multiple dosing with immediate-release fluvoxamine maleate tablets (50 mg given twice daily) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other.

Carbamazepine: Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of immediate-release fluvoxamine maleate tablets and carbamazepine.

Clozapine: Elevated serum levels of clozapine have been reported in patients taking immediate-release fluvoxamine maleate tablets and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be dose related, the risk of these adverse events may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when LUVOX® CR Capsules and clozapine are used concurrently.

Lithium: As with other serotonergic drugs, lithium may enhance the serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of immediate-release fluvoxamine maleate tablets and lithium.

Lorazepam: A study of multiple doses of immediate-release fluvoxamine maleate tablets (50 mg given twice daily) in healthy male volunteers (N=12) and a single dose of lorazepam (4 mg single dose) indicated no significant pharmacokinetic interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone.

Methadone: Significantly increased methadone (plasma level:dose) ratios have been reported when immediate-release fluvoxamine maleate tablets were administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in one patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient.

Ramelteon: When immediate-release fluvoxamine maleate tablets 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ramelteon 16 mg and immediate-release fluvoxamine maleate tablets, the AUC for ramelteon increased approximately 190-fold and the C_{max} increased approximately 70-fold compared to ramelteon administered alone. Ramelteon should not be used in combination with LUVOX® CR Capsules (see **WARNINGS**).

Serotonergic Drugs: Based on the mechanism of action of LUVOX® CR Capsules and the potential for serotonin syndrome, caution is advised when fluvoxamine is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol or St. John's Wort (see **WARNINGS – Serotonin Syndrome**). The concomitant use of LUVOX® CR Capsules with other SSRIs, SNRIs, or tryptophan is not recommended (see **PRECAUTIONS – Drug Interactions**).

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, etc.) is clinically warranted, appropriate observation of the patient is advised.

Tacrine: In a study of 13 healthy, male volunteers, a single 40 mg dose of tacrine added to immediate-release fluvoxamine maleate tablets 100 mg/day administered at steady state was associated with 5-fold and 8-fold increases in tacrine C_{max} and AUC, respectively, compared to the administration of tacrine alone. Five subjects experienced nausea, vomiting, sweating, and diarrhea following co-administration, consistent with the cholinergic effects of tacrine.

Thioridazine: See **CONTRAINDICATIONS** and **WARNINGS**.

Triptans: There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of fluvoxamine with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS – Serotonin Syndrome**).

Tizanidine: See **CONTRAINDICATIONS** and **WARNINGS**.

Tricyclic Antidepressants (TCAs): Significantly increased plasma TCA levels have been reported with the co-administration of immediate-release fluvoxamine maleate tablets and amitriptyline, clomipramine, or imipramine. Caution is indicated with the co-administration of LUVOX® CR Capsules and TCAs; plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced.

Tryptophan: Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with the co-administration of immediate-release fluvoxamine maleate tablets and tryptophan.

Other Drugs:

Theophylline: See **WARNINGS**.

Warfarin: See **WARNINGS**.

Alosetron: Because alosetron is metabolized by a variety of hepatic CYP drug metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. Fluvoxamine is a known potent inhibitor of CYP1A2 and also inhibits CYP3A4, CYP2C9, and CYP2C19. In a pharmacokinetic study, 40 healthy female subjects received fluvoxamine in escalating doses from 50 mg to 200 mg a day for 16 days, with co-administration of alosetron 1 mg on the last day. Fluvoxamine increased mean alosetron plasma concentration (AUC) approximately 6-fold and prolonged the half-life by approximately 3-fold. (see **CONTRAINDICATIONS**, **PRECAUTIONS**, and Lotronex™ (alosetron) package insert).

Digoxin: Administration of immediate-release fluvoxamine maleate tablets 100 mg daily for 18 days (N=8) did not significantly affect the pharmacokinetics of a 1.25 mg single intravenous dose of digoxin.

Diltiazem: Bradycardia has been reported with the co-administration of immediate-release fluvoxamine maleate tablets and diltiazem.

Propranolol and Other Beta-Blockers: Co-administration of immediate-release fluvoxamine maleate tablets 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean 5-fold increase (range 2-fold to 17-fold) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure.

One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with the co-administration of immediate-release fluvoxamine maleate tablets and metoprolol.

If propranolol or metoprolol is co-administered with LUVOX® CR Capsules, a reduction in the initial beta-blocker dose and more cautious dose titration are recommended. No dosage adjustment is required for LUVOX® CR Capsules.

Co-administration of immediate-release fluvoxamine maleate tablets 100 mg per day with atenolol 100 mg per day (N=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol, which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion.

Drugs That Interfere With Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin): Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin should be carefully monitored when LUVOX® CR Capsules is initiated or discontinued.

Effects of Smoking on Fluvoxamine Metabolism: Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers.

Electroconvulsive Therapy (ECT): There are no clinical studies establishing the benefits or risks of combined use of ECT and fluvoxamine maleate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 (females) or 26 (males) months. The daily doses in the high dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is approximately 6 times the maximum human daily dose on a mg/m^2 basis.

Mutagenesis: No evidence of genotoxic potential was observed in a mouse micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation.

Impairment of Fertility: In a study in which male and female rats were administered fluvoxamine (60 mg/kg, 120 mg/kg, or 240 mg/kg) orally prior to and during mating and gestation, fertility was impaired at oral doses of 120 mg/kg or greater, as evidenced by increased latency to mating, decreased sperm count, decreased epididymal weight, and decreased pregnancy rate. In addition, the numbers of implantations and embryos were decreased at the highest dose. The no effect dose for fertility impairment was 60 mg/kg (approximately 2 times the maximum recommended human dose [MRHD] on a mg/m^2 basis).

Pregnancy

Teratogenic Effects – Pregnancy Category C: When pregnant rats were given fluvoxamine (60 mg/kg, 120 mg/kg, or 240 mg/kg) orally throughout the period of organogenesis, developmental toxicity in the form of increased embryofetal death and increased incidences of fetal eye abnormalities (folded retinas) was observed at doses of 120 mg/kg or greater. Decreased fetal body weight was seen at the high dose. The no effect dose for developmental toxicity in this study was 60 mg/kg (approximately 2 times the maximum recommended human dose [MRHD] on a mg/m^2 basis).

In a study in which pregnant rabbits were administered doses of up to 40 mg/kg (approximately 2 times the MRHD on a mg/m^2 basis) orally during organogenesis, no adverse effects on embryofetal development were observed.

In other reproductive studies in which female rats were dosed orally during pregnancy and lactation (5 mg/kg, 20 mg/kg, 80 mg/kg, or 160 mg/kg), increased pup mortality at birth was seen at doses of 80 mg/kg or greater and decreases in pup body weight and survival were observed at all doses (low effect dose approximately 0.1 times the MRHD on a mg/m^2 basis).

Nonteratogenic Effects*:* Neonates exposed to immediate-release fluvoxamine maleate tablets and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs) late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. These findings are based on Postmarketing reports. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs or SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS**).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN is associated with substantial neonatal morbidity and mortality. In a case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately 6-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. PPHN occurs in 1-2 per 1000 live births in the general population.

When treating a pregnant woman with LUVOX® CR Capsules during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Labor and Delivery

The effect of fluvoxamine on labor and delivery in humans is unknown.

Nursing Mothers

Fluvoxamine is secreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants from LUVOX® CR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

LUVOX® CR Capsules have not been evaluated in pediatric patients (see **BOXED WARNING**). The efficacy of fluvoxamine maleate administered as immediate-release tablets for the treatment of OCD, was demonstrated in a 10-week multicenter placebo-controlled study with 120 outpatients ages 8-17. In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment for up to another one to three years, equivalent to 94 patient years. The adverse event profile observed in that study was generally similar to that observed in adult studies with immediate-release fluvoxamine maleate tablets (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.

The risks if any that may be associated with fluvoxamine's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents derives from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term fluvoxamine use on the growth, cognitive behavioral development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of fluvoxamine to have adverse effects in chronic use (see **WARNINGS – Clinical Worsening and Suicide Risk**).

Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established (see **BOXED WARNING** and **WARNINGS—Clinical Worsening and Suicide Risk**). Anyone considering the use of LUVOX® CR Capsules in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

Approximately 230 patients and 5 patients participating in controlled premarketing studies with immediate-release fluvoxamine maleate tablets and LUVOX® CR Capsules, respectively, were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, fluvoxamine has been associated with several cases of clinically significant hyponatremia in elderly patients (see **PRECAUTIONS – General**). Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see **Pharmacokinetics** under **CLINICAL PHARMACOLOGY**), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX® CR Capsules should be slowly titrated during initiation of therapy. SSRIs and

SNRIs, including LUVOX® CR Capsules, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS, Hyponatremia**).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Of the 279 patients with social anxiety disorder and 124 patients with OCD treated with LUVOX® CR Capsules in controlled clinical trials, 26% and 19% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) are provided in Table 4.

TABLE 4. ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN SOCIAL ANXIETY DISORDER AND OCD POPULATIONS

	Percentage of Patients			
	Social Anxiety Disorder		Obsessive Compulsive Disorder	
Body System / Adverse Event	LUVOX® CR	Placebo	LUVOX® CR	Placebo
Body as a Whole				
Asthenia	4	<1	2	0
Headache	3	<1	–	–
Abdominal Pain	1	0	–	–
Pain	–	–	2	0
Digestive				
Nausea	8	<1	6	0
Diarrhea	3	0	2	0
Anorexia[1]	2	0	–	–
Dyspepsia	–	–	2	0
Nervous System				
Insomnia	5	<1	5	2
Somnolence	5	<1	4	0
Anxiety	4	<1	2	<1
Dizziness	4	0	3	0
Abnormal Thinking	2	<1	–	–
Nervousness	2	<1	–	–
Depression	1	0	–	–
Agitation	1	0	–	–
Paresthesia	1	0	–	–
Tremor	1	0	–	–
Skin and Appendages				
Sweating	1	0	–	–

[1]Includes, but is not limited to, loss of appetite and decreased appetite.

Incidence in Controlled Trials

***Commonly Observed Adverse Events**:* LUVOX® CR Capsules have been studied in two controlled trials of social anxiety disorder (N=279) and one trial of OCD (N=124). In general, adverse event rates were similar in the two data sets as well as in a study of pediatric patients with OCD treated with immediate-release fluvoxamine maleate tablets. The most commonly observed adverse events associated with the use of LUVOX® CR Capsules and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) for patients in social anxiety disorder and in OCD derived from Table 5 were: *abnormal ejaculation, anorexia, anorgasmia asthenia, diarrhea, nausea, somnolence, sweating and tremor*. In addition, the following events occurred in the social anxiety disorder population: *dyspepsia, dizziness, insomnia, and yawning*. In the OCD population, the following additional events occurred: *accidental injury, anxiety, decreased libido, myalgia, pharyngitis, and vomiting*. In a study evaluating immediate-

release fluvoxamine maleate tablets in pediatric patients with OCD, the following additional events were identified using the above rule: *agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash.*

Adverse Events Occurring at an Incidence of 2%: Table 5 enumerates adverse events that occurred in adults at a frequency of 2% or more, and were more frequent than in the placebo group, among patients treated with LUVOX® CR Capsules in two short-term, placebo-controlled social anxiety disorder trials (12 week) and one short-term placebo-controlled OCD trial (12 week) and in which patients were dosed once-a-day in a range of 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing health care provider with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

TABLE 5. TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES BY BODY SYSTEM IN ADULT SOCIAL ANXIETY DISORDER AND OCD POPULATIONS[1]

	Percentage of Patients Reporting Event			
	Social Anxiety Disorder		Obsessive Compulsive Disorder	
Body System /Adverse Event	LUVOX® CR N=279	Placebo N=276	LUVOX® CR N=124	Placebo N=124
Body as a Whole				
Headache	35	30	32	31
Asthenia	24	10	26	8
Pain[2]	–	–	10	8
Abdominal Pain	5	4	–	–
Accidental Injury	–	–	5	3
Chest Pain	3	1	–	–
Viral Infection	–	–	2	<1
Cardiovascular				
Palpitation	3	1	–	–
Vasodilatation	2	<1	–	–
Hypertension	–	–	2	<1
Digestive System				
Nausea	39	11	34	13
Diarrhea	14	5	18	8
Anorexia[3]	14	1	13	5
Dyspepsia	10	4	8	5
Constipation	6	5	4	<1
Vomiting	–	–	6	2
Tooth Disorder	–	–	2	<1
Liver Function Test Abnormal	2	<1	–	–
Gingivitis	–	–	2	0
Hemic and Lymphatic				
Ecchymosis	–	–	4	2
Metabolic and Nutritional Disorders				
Weight Loss	–	–	2	<1
Musculoskeletal				
Myalgia	–	–	5	2
Nervous System				
Insomnia	32	13	35	20

Body System /Adverse Event	Percentage of Patients Reporting Event			
	Social Anxiety Disorder		Obsessive Compulsive Disorder	
	LUVOX® CR N=279	Placebo N=276	LUVOX® CR N=124	Placebo N=124
Somnolence	26	9	27	11
Dizziness	15	7	12	10
Dry Mouth	11	8	10	9
Nervousness	10	9	–	–
Libido Decreased	6	4	6	2
Male	8	6	10	5
Female	4	3	4	1
Anxiety	8	5	6	2
Tremor	8	<1	6	0
Abnormal Thinking	3	2	3	<1
Abnormal Dreams	3	2	–	–
Agitation	3	<1	2	<1
Hypertonia	2	1	–	–
Apathy	–	–	3	0
Paresthesia	3	2	–	–
Neurosis	–	–	2	<1
Twitching	–	–	2	0
Respiratory System				
Pharyngitis	–	–	6	<1
Yawn	5	<1	2	0
Laryngitis	–	–	3	0
Bronchitis	2	1	–	–
Epistaxis	–	–	2	0
Skin				
Sweating	6	2	7	<1
Acne	–	–	2	0
Special Senses				
Taste Perversion	2	<1	2	<1
Amblyopia	–	–	2	<1
Urogenital				
Abnormal Ejaculation	11	2	10	0
Anorgasmia	5	1	5	0
Male	4	2	4	0
Female	5	0	5	0
Menorrhagia	–	–	3	0
Sexual Function Abnormal	3	<1	2	<1
Male	2	1	4	3
Female	3	0	0	0
Urinary Tract Infection	2	<1	–	–
Polyuria	–	–	2	<1

[1] Events for which fluvoxamine maleate incidence was equal to or less than placebo include the following for social anxiety disorder patients: abdominal pain, accidental injury, back pain, flu syndrome, infection, pain, flatulence, pharyngitis, rhinitis, rash, and dysmenorrhea. In OCD patients the following events were seen: abdominal pain, flu syndrome, infection, palpitation, flatulence, increased appetite, weight gain, abnormal dreams, amnesia, hypertonia, nervousness, paresthesia, increased cough, dyspnea, rhinitis, and ear pain.

[2] Term includes body aches/pains, dental pain, pain from surgery, unspecified pain, and general pain secondary to injuries (sprains, fractures).

[3] Includes, but is not limited to, loss of appetite and decreased appetite.

Other Adverse Events in OCD Pediatric Population

In pediatric patients (N=57) treated with immediate-release fluvoxamine maleate tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 5. However, the following adverse events, not appearing in Table 5, were reported in two or more of the pediatric patients and were more frequent with immediate-release fluvoxamine maleate tablets than with placebo: cough increase, dysmenorrhea, emotional lability, fever, flatulence, flu syndrome, hyperkinesia, infection, manic reaction, rash, rhinitis, and sinusitis.

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder and with aging, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and health care providers may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

Table 6 displays the incidence of sexual side effects reported by at least 2% of patients taking LUVOX CR® capsules in placebo-controlled trials of social anxiety disorder and OCD.

TABLE 6. PERCENTAGE OF PATIENTS REPORTING SEXUAL ADVERSE EVENTS IN PLACEBO-CONTROLLED TRIALS

	LUVOX® CR N=403	PLACEBO N=400
Abnormal Ejaculation	11	2
Anorgasmia		
Male	4	1
Female	5	0
Impotence	2	3
Libido Decreased		
Male	8	5
Female	4	2
Sexual Function Abnormal		
Male	3	5
Female	2	0

Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, health care providers should routinely inquire about such possible side effects.

Weight and Vital Sign Changes

No statistically significant differences in weight gain or loss were found between patients treated with LUVOX® CR Capsules or placebo. Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX® CR Capsules versus placebo groups in separate short-term trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various measures of vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes

Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX® CR Capsules versus placebo groups in separate short-term trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes

Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX® CR Capsules and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

Other Events Observed During the Premarketing Evaluation of Fluvoxamine

During premarketing clinical trials conducted in North America and Europe, multiple doses of immediate-release fluvoxamine maleate tablets were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standard event categories.

In the tabulations which follow, a COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 2, which tabulates incidence rates of common adverse experiences in placebo-controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring between 1/100 and 1/1000 patients; and rare adverse events are those occurring in less than 1/1000 patients.

Body as a Whole**:* **Frequent*: malaise; **Infrequent:** allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; **Rare:** cyst, pelvic pain, sudden death.

Cardiovascular System: **Frequent:** hypertension, hypotension, syncope; **Infrequent:** angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes; **Rare:** AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles.

Digestive System: **Frequent:** elevated liver transaminases; **Infrequent:** colitis, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, glossitis, hemorrhoids, melena, rectal hemorrhage, stomatitis; **Rare:** biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice.

Endocrine System: **Infrequent:** hypothyroidism; **Rare:** goiter.

Hemic and Lymphatic Systems: **Infrequent:** anemia, leukocytosis, lymphadenopathy, thrombocytopenia; **Rare:** leukopenia, purpura.

Metabolic and Nutritional Systems: **Frequent:** edema, weight gain; **Infrequent:** dehydration, hypercholesterolemia; **Rare:** diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased.

Musculoskeletal System: **Infrequent:** arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis; **Rare:** arthrosis, myopathy, pathological fracture.

Nervous System: **Frequent:** amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction; **Infrequent:** agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; **Rare:** akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome.

Respiratory System: **Frequent:** cough increased, sinusitis; **Infrequent:** asthma, bronchitis, hoarseness, hyperventilation; **Rare:** apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia.

Skin: **Infrequent:** alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin discoloration, urticaria.

Special Senses: **Infrequent:** accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** corneal ulcer, retinal detachment.

Urogenital System**: Infrequent:** anuria, breast pain, cystitis, delayed menstruation[1], dysuria, female lactation[1], hematuria, menopause[1], metrorrhagia[1], nocturia, premenstrual syndrome[1], urinary incontinence, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginitis[1]; **Rare:** kidney calculus, hematospermia[2], oliguria.

[1] Based on the number of females.
[2] Based on the number of males.

Postmarketing Reports

Voluntary reports of adverse events in patients taking fluvoxamine maleate immediate-release tablets that have been received since market introduction and are of unknown causal relationship to fluvoxamine use include: acute renal failure, agranulocytosis, amenorrhea, anaphylactic reaction, angioedema, aplastic anemia, bullous eruption, Henoch-Schoenlein purpura, hepatitis, hyponatremia, ileus, laryngismus, neuropathy, pancreatitis, porphyria, priapism, serotonin syndrome, severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, and ventricular tachycardia (including torsades de pointes).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
LUVOX® CR is not a controlled substance.

Physical and Psychological Dependence

The potential for abuse, tolerance and physical dependence with immediate release fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX® CR Capsules were not systematically evaluated in controlled clinical

trials. LUVOX® CR Capsules were not systematically studied in clinical trials for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It should be noted, however, that patients at risk for drug dependency were systematically excluded from investigational studies of immediate-release fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, health care providers should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of LUVOX® CR misuse or abuse (i.e., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Exposure to immediate-release fluvoxamine maleate tablets includes over 45,000 patients treated in clinical trials and an estimated exposure of 50,000,000 patients treated during worldwide marketing experience (end of 2005). Of the 539 cases of deliberate or accidental overdose involving fluvoxamine reported from this population, there were 55 deaths. Of these, 9 were in patients thought to be taking immediate-release fluvoxamine tablets alone and the remaining 46 were in patients taking fluvoxamine along with other drugs. Among non-fatal overdose cases, 404 patients recovered completely. Five patients experienced adverse sequelae of overdosage, to include persistent mydriasis, unsteady gait, hypoxic encephalopathy, kidney complications (from trauma associated with overdose), bowel infarction requiring a hemicolectomy, and vegetative state. In 13 patients, the outcome was provided as abating at the time of reporting. In the remaining 62 patients, the outcome was unknown. The largest known ingestion of fluvoxamine immediate-release tablets involved 12,000 mg (equivalent to 2 to 3 months' dosage). The patient fully recovered. However, ingestions as low as 1,400 mg have been associated with lethal outcome, indicating considerable prognostic variability.

In the controlled clinical trials with 403 patients treated with LUVOX® CR Capsules, there was one nonfatal intentional overdose.

Commonly (≥5%) observed adverse events associated with fluvoxamine maleate overdose include gastrointestinal complaints (nausea, vomiting, and diarrhea), coma, hypokalemia, hypotension, respiratory difficulties, somnolence, and tachycardia. Other notable signs and symptoms seen with immediate-release fluvoxamine maleate overdose (single or multiple drugs) include bradycardia, ECG abnormalities, (such as heart arrest, QT interval prolongation, first degree atrioventricular block, bundle branch block, and junctional rhythm), convulsions, dizziness, liver function disturbances, tremor, and increased reflexes.

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluvoxamine are known.

A specific caution involves patients taking, or recently having taken, fluvoxamine maleate who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see ***Tricyclic Antidepressants (TCAs)*** under **PRECAUTIONS**).

In managing overdosage, consider the possibility of multiple drug involvement. The health care provider should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Social Anxiety Disorder and OCD (Obsessive Compulsive Disorder)

The recommended starting dose for LUVOX® CR Capsules in adult patients is 100 mg once per day. LUVOX® CR Capsules should be administered, with or without food, as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX® CR Capsules in social anxiety disorder and OCD, patients were titrated in 50 mg increments within a dose range of 100 mg/day to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every week, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day.

Capsules should not be crushed or chewed.

Special Populations

Dosage for Elderly or Hepatically Impaired Patients

Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to titrate slowly following the initial dose of 100 mg in these patient groups.

Treatment of Pregnant Women During the Third Trimester

No neonates have been exposed to LUVOX® CR Capsules. Neonates exposed to immediate-release fluvoxamine maleate tablets and other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with LUVOX® CR Capsules during the third trimester, the health care provider should carefully consider the potential risks and benefits of treatment. The health care provider may consider tapering LUVOX® CR Capsules in the third trimester.

Maintenance/Continuation of Extended Treatment

Although the efficacy of LUVOX® CR Capsules beyond 12 weeks of dosing for social anxiety disorder and OCD has not been documented in controlled trials, social anxiety disorder and OCD are chronic conditions, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

Switching Patients To or From a Monoamine Oxidase Inhibitor:

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with LUVOX® CR Capsules. Similarly, at least 14 days should be allowed after stopping LUVOX CR Capsules before starting an MAOI.

Discontinuation of Treatment with LUVOX® CR Capsules

Symptoms associated with discontinuation of other SSRIs or SNRIs have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the health care provider may continue decreasing the dose but at a more gradual rate.

TABULAR COMPARISON OF LUVOX® CR TO OTHER FDA-APPROVED PRODUCTS FOR THE TREATMENT OF SAD AND OCD

Note: All information in these tables was obtained from the product labels for each drug.

TABLE 7. DESCRIPTION

BRAND	CHEMICAL CLASS	MECHANISM OF ACTION
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	Selective serotonin reuptake inhibitor	The mechanism of action of fluvoxamine maleate in obsessive compulsive disorder (OCD) is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. Fluvoxamine has been shown to be a potent inhibitor of the serotonin reuptake transporter in preclinical studies, both *in vitro* and *in vivo*.
PAXIL® (paroxetine hydrochloride)	Selective serotonin reuptake inhibitor	The efficacy of paroxetine in the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT).
PAXIL® CR (paroxetine hydrochloride) controlled release	Selective serotonin reuptake inhibitor	The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder (PMDD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT).
Prozac® (fluoxetine hydrochloride)	Selective serotonin reuptake inhibitor	The antidepressant, antiobsessive compulsive, and antibulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin.
ZOLOFT® (sertraline hydrochloride)	Selective serotonin reuptake inhibitor	The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT).
EFFEXOR XR® (venlafaxine hydrochloride)	Selective norepinephrine reuptake inhibitor	The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.
Anafranil® (clomipramine hydrochloride)	Tricyclic	Clomipramine hydrochloride is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but clomipramine's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.

TABLE 8. INDICATIONS

BRAND	OCD	SAD	MDD	PD	GAD	PTSD	PMDD	BN
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	X	X						
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	X							
PAXIL® (paroxetine hydrochloride)	X	X	X	X	X	X		
PAXIL® CR (paroxetine hydrochloride) controlled release		X	X	X			X	
Prozac® (fluoxetine hydrochloride)	X		X	X				X
ZOLOFT® (sertraline hydrochloride)	X	X	X	X		X	X	
EFFEXOR XR® (venlafaxine hydrochloride)		X	X	X	X			
Anafranil® (clomipramine hydrochloride)	X							

BN=bulimia nervosa; GAD=generalized anxiety disorder; MDD=major depressive disorder; OCD=obsessive compulsive disorder; PD=panic disorder; PMDD=premenstrual dysphoric disorder; PTSD=post-traumatic stress disorder; SAD=social anxiety disorder.

TABLE 9. BIOAVAILABLITY AND ABSORPTION

BRAND	BIOAVAILABILITY AND ABSORPTION
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	In the single-dose crossover study, mean C_{max} was 38% lower and relative bioavailability was 84% for LUVOX® CR Capsules versus immediate-release fluvoxamine maleate tablets.
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	The absolute bioavailability of fluvoxamine maleate is 53%. In a dose proportionality study involving fluvoxamine maleate at 100, 200, and 300 mg/day for 10 consecutive days in 30 normal volunteers, steady state was achieved after about a week of dosing.
PAXIL® (paroxetine hydrochloride)	Paroxetine is equally bioavailable from the oral suspension and tablet. Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (N=15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately 10 days for most subjects, although it may take substantially longer in an occasional patient.
PAXIL® CR (paroxetine hydrochloride) controlled release	Tablets of PAXIL CR contain a degradable polymeric matrix (GEOMATRIX™) designed to control the dissolution rate of paroxetine over a period of approximately 4 to 5 hours. In addition to controlling the rate of drug release *in vivo*, an enteric coat delays the start of drug release until tablets of PAXIL CR have left the stomach.
Prozac® (fluoxetine hydrochloride)	The Pulvule, tablet, oral solution, and Prozac Weekly capsule dosage forms of fluoxetine are bioequivalent. Prozac Weekly capsules, a delayed-release formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of fluoxetine 1 to 2 hours relative to the immediate-release formulations.
ZOLOFT® (sertraline hydrochloride)	The single dose bioavailability of sertraline tablets is approximately equal to an equivalent dose of solution.

BRAND	BIOAVAILABILITY AND ABSORPTION
EFFEXOR XR® (venlafaxine hydrochloride)	On the basis of mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%.
Anafranil® (clomipramine hydrochloride)	Clomipramine from Anafranil capsules is as bioavailable as clomipramine from a solution.

TABLE 10. PEAK PLASMA CONCENTRATION AND DOSE PROPORTIONALITY

BRAND	PEAK PLASMA CONCENTRATION AND DOSE PROPORTIONALITY
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	In a multiple-dose proportionality study, LUVOX® CR Capsules were administered over a dose range of 100 to 300 mg/day to 20 healthy volunteers. Steady-state plasma concentrations were achieved within a week of dosing. Mean maximum plasma concentrations were 47 ng/mL, 161 ng/mL, and 319 ng/mL, respectively, at the 100 mg, 200 mg, and 300 mg administered dose levels. Fluvoxamine exhibited nonlinear pharmacokinetics producing disproportionately higher concentrations over the dose range. The AUC and C_{max} values increased 5.7-fold following the 3-fold increase in dose from 100 mg to 300 mg.
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	Maximum plasma concentrations at steady state occurred within 3 to 8 hours of dosing and reached concentrations averaging 88, 283, and 546 ng/mL, respectively. Thus, fluvoxamine had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.
PAXIL® (paroxetine hydrochloride)	At steady state, mean values of C_{max}, T_{max}, C_{min}, and $T_{½}$ were 61.7 ng/mL (CV 45%), 5.2 hr (CV 10%), 30.7 ng/mL (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on AUC_{0-24} was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.
PAXIL® CR (paroxetine hydrochloride) controlled release	In a study in which normal male and female subjects (N=23) received single oral doses of PAXIL CR at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg, and 50 mg), paroxetine C_{max} and AUC_{0-inf} increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and AUC_{0-inf} values at these doses were 2.0, 5.5, 9.0, and 12.5 ng/mL, and 121, 261, 338, and 540 ng•hr./mL, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations.
Prozac® (fluoxetine hydrochloride)	In man, following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.
ZOLOFT® (sertraline hydrochloride)	In man, following oral once-daily dosing over the range of 50 to 200 mg for 14 days, mean peak plasma concentrations (C_{max}) of sertraline occurred between 4.5 to 8.4 hours post-dosing. In a relative bioavailability study comparing the pharmacokinetics of 100 mg sertraline as the oral solution to a 100 mg sertraline tablet in 16 healthy adults, the solution to tablet ratio of geometric mean AUC and C_{max} values were 114.8% and 120.6%, respectively. 90% confidence intervals (CI) were within the range of 80% to 125% with the exception of the upper 90% CI limit for C_{max} which was 126.5%. Linear dose-proportional pharmacokinetics were demonstrated in a single dose study in which the C_{max} and area under the plasma concentration time curve (AUC) of sertraline were proportional to dose over a range of 50 to 200 mg. Consistent with the terminal elimination half-life, there is an approximately two-fold accumulation, compared to a single dose, of sertraline with repeated dosing over a 50 to 200 mg dose range.
EFFEXOR XR® (venlafaxine hydrochloride)	Steady-state concentrations of venlafaxine and O-desmethylvenlafaxine (ODV) in plasma are attained within 3 days of oral multiple dose therapy. Administration of Effexor XR (150 mg q24 hours) generally resulted in lower C_{max} (150 ng/mL for venlafaxine and 260 ng/mL for ODV) and later T_{max} (5.5 hours for venlafaxine and 9 hours for ODV) than for immediate-release venlafaxine tablets (C_{max} for immediate release 75 mg q12 hours were 225 ng/mL for venlafaxine and 290 ng/mL for ODV; T_{max} were 2 hours for venlafaxine and 3 hours for ODV). When equal daily doses of venlafaxine were administered as either an immediate release tablet or the extended-release capsule, the exposure to both venlafaxine and ODV was similar for the two treatments, and the fluctuation in plasma concentrations was slightly lower with the Effexor XR capsule. Effexor XR, therefore, provides a slower rate of absorption, but the same extent of absorption compared with the immediate release tablet.
Anafranil® (clomipramine hydrochloride)	After a single 50-mg oral dose, maximum plasma concentrations of clomipramine occur within 2 to 6 hours (mean, 4.7 hr) and range from 56 ng/mL to 154 ng/mL (mean, 92 ng/mL). In a dose proportionality study involving multiple clomipramine doses, steady-state plasma concentrations (C_{ss}) and area-under-plasma-concentration-time curves (AUC) of clomipramine and clomipramine's major active metabolite, desmethylclomipramine, were not proportional to dose over the ranges evaluated, i.e., between 25 to 100 mg/day and between 25 to 150 mg/day, although C_{ss} and AUC are approximately linearly related to dose between 100 to 150 mg/day. The relationship between dose and clomipramine / desmethylclomipramine concentrations at higher daily doses has not been systematically assessed, but if there is significant dose dependency at doses above 150 mg/day, there is the potential for dramatically higher C_{ss} and AUC even for

BRAND	PEAK PLASMA CONCENTRATION AND DOSE PROPORTIONALITY
	patients dosed within the recommended range. This may pose a potential risk to some patients. After multiple daily doses of 150 mg of Anafranil, steady-state maximum plasma concentrations range from 94 ng/mL to 339 ng/mL (mean, 218 ng/mL) for clomipramine and from 134 ng/mL to 532 ng/mL (mean, 274 ng/mL) for desmethylclomipramine. Additional information from a rising dose study of doses up to 250 mg suggests that desmethylclomipramine may exhibit nonlinear pharmacokinetics over the usual dosing range. At a dose of Anafranil 200 mg, subjects who had a single blood sample taken approximately 9 to 22 hours (median 16 hours) after the dose had plasma concentrations of up to 605 ng/mL for clomipramine, 781 ng/mL for desmethylclomipramine, and 1386 ng/mL for both.

TABLE 11. ADMINISTRATION WITH FOOD

BRAND	ADMINISTRATION WITH FOOD
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	Food caused the mean AUC and C_{max} of fluvoxamine to increase only slightly; therefore, administration of LUVOX® CR Capsules with food does not significantly affect the absorption of fluvoxamine.
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	Oral bioavailability is not significantly affected by food.
PAXIL® (paroxetine hydrochloride)	The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the C_{max} was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.
PAXIL® CR (paroxetine hydrochloride) controlled release	The bioavailability of 25 mg PAXIL CR is not affected by food.
Prozac® (fluoxetine hydrochloride)	Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant.
ZOLOFT® (sertraline hydrochloride)	The effects of food on the bioavailability of the sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, AUC was slightly increased when drug was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration (T_{max}) decreased from 8 hours post-dosing to 5.5 hours. For the oral concentrate, T_{max} was slightly prolonged from 5.9 hours to 7.0 hours with food.
EFFEXOR XR® (venlafaxine hydrochloride)	Food did not affect the bioavailability of venlafaxine or its active metabolite, O-desmethylvenlafaxine.
Anafranil® (clomipramine hydrochloride)	The bioavailability of clomipramine from capsules is not significantly affected by food.

TABLE 12. DISTRIBUTION – BINDING TO PLASMA PROTEINS

BRAND	BINDING TO PLASMA PROTEINS
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 ng/mL to 2000 ng/mL.
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.
Prozac® (fluoxetine hydrochloride)	Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound *in vitro* to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important.
ZOLOFT® (sertraline hydrochloride)	*In vitro* protein binding studies performed with radiolabeled ^{3}H-sertraline showed that sertraline is highly bound to serum proteins (98%) in the range of 20 to 500 ng/mL. However, at up to 300 and 200 ng/mL concentrations, respectively, sertraline and N-desmethylsertraline did not alter the plasma protein binding of two other highly protein bound drugs, viz., warfarin, and propranolol.
EFFEXOR XR® (venlafaxine hydrochloride)	Venlafaxine and O-desmethylvenlafaxine are minimally bound at therapeutic concentrations to plasma proteins (27% and 30%, respectively).
Anafranil® (clomipramine hydrochloride)	The protein binding of clomipramine is approximately 97%, principally to albumin, and is independent of clomipramine concentration. The interaction between clomipramine and other highly protein-bound drugs has not been fully evaluated, but may be important.

TABLE 13. DISTRIBUTION – VOLUME OF DISTRIBUTION

BRAND	VOLUME OF DISTRIBUTION
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution.
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.
Prozac® (fluoxetine hydrochloride)	Unknown
ZOLOFT® (sertraline hydrochloride)	Unknown
EFFEXOR XR® (venlafaxine hydrochloride)	Mean ± SD apparent (steady-state) volume of distribution of venlafaxine and O-desmethylvenlafaxine is 7.5 ± 3.7 and 5.7 ± 1.8 L/kg, respectively.
Anafranil® (clomipramine hydrochloride)	Clomipramine distributes into cerebrospinal fluid (CSF) and brain and into breast milk. Desmethylclomipramine also distributes into CSF, with a mean CSF/plasma ratio of 2.6.

TABLE 14. METABOLISM

BRAND	METABOLIC PATHWAY
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabeled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound).
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions.
Prozac® (fluoxetine hydrochloride)	Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, and the tricyclic antidepressants. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit. Because fluoxetine’s metabolism, like that of a number of other compounds including tricyclic antidepressants and other selective serotonin reuptake inhibitors, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the tricyclic antidepressants) may lead to drug interactions.
ZOLOFT® (sertraline hydrochloride)	Sertraline undergoes extensive first pass metabolism. The principal initial pathway of metabolism for sertraline is N-demethylation. Both *in vitro* biochemical and *in vivo* pharmacological testing have shown N-desmethylsertraline to be substantially less active than sertraline. Both sertraline and N-desmethylsertraline undergo oxidative deamination and subsequent reduction hydroxylation, and glucuronide conjugation.
EFFEXOR XR® (venlafaxine hydrochloride)	Following absorption, venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to O-desmethylvenlafaxine, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites. *In vitro* studies indicate that the formation of O-desmethylvenlafaxine is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels (“poor metabolizers”) had increased levels of venlafaxine and reduced levels of O-desmethylvenlafaxine compared to people with normal CYP2D6 (“extensive metabolizers”). The differences between the CYP2D6 poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and O-desmethylvenlafaxine is similar in the two groups and venlafaxine and O-desmethylvenlafaxine are pharmacologically approximately equiactive and equipotent.
Anafranil® (clomipramine hydrochloride)	Clomipramine is extensively biotransformed to desmethylclomipramine and other metabolites and their glucuronide conjugates. Desmethylclomipramine is pharmacologically active, but its effects on OCD behaviors are unknown.

TABLE 15. ELIMINATION

BRAND	ELIMINATION HALF-LIFE	EXCRETION ROUTE
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	After administration of a 100 mg, single oral dose of LUVOX® CR Capsules, the mean plasma half-life of fluvoxamine in healthy male and female volunteers was 16.3 hours.	Following a ^{14}C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours.
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	The mean plasma half-life of fluvoxamine at steady state after multiple oral doses of 100 mg/day in healthy, young volunteers was 15.6 hours.	Approximately 2% of fluvoxamine was excreted in urine unchanged.
PAXIL® (paroxetine hydrochloride)	The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets daily for 30 days of PAXIL.	Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.
PAXIL® CR (paroxetine hydrochloride) controlled release	The mean elimination half-life was 15 to 20 hours throughout a range of single doses of PAXIL CR (12.5 mg, 25 mg, 37.5 mg, and 50 mg).	
Prozac® (fluoxetine hydrochloride)	The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used.	The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.
ZOLOFT® (sertraline hydrochloride)	The average terminal elimination half-life of plasma sertraline is about 26 hours. N-desmethylsertraline, the major metabolite of sertraline, has a plasma terminal elimination half-life of 62 to 104 hours.	In a study of radiolabeled sertraline involving two healthy male subjects, sertraline accounted for less than 5% of the plasma radioactivity. About 40% to 45% of the administered radioactivity was recovered in urine in 9 days. Unchanged sertraline was not detectable in the urine. For the same period, about 40% to 45% of the administered radioactivity was accounted for in feces, including 12% to 14% unchanged sertraline.
EFFEXOR XR® (venlafaxine hydrochloride)	Mean ± SD apparent elimination half-life of venlafaxine and O-didesmethylvenlafaxine is 5 ± 2 and 11 ± 2 hours, respectively.	Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated O-didesmethylvenlafaxine (29%), conjugated O-didesmethylvenlafaxine (26%), or other minor inactive metabolites (27%). Renal elimination of venlafaxine and its metabolites is thus the primary route of excretion.
Anafranil® (clomipramine hydrochloride)	After a 150-mg dose, the half-life of clomipramine ranges from 19 hours to 37 hours (mean, 32 hr) and that of desmethylclomipramine ranges from 54 hours to 77 hours (mean, 69 hr).	Metabolites are excreted in urine and feces following biliary elimination. After a 25-mg radiolabeled dose of clomipramine in two subjects, 60% and 51%, respectively, of the dose were recovered in the urine and 32% and 24%, respectively, in feces. In the same study, the combined urinary recoveries of clomipramine and desmethylclomipramine were only about 0.8% to 1.3% of the dose administered. Clomipramine does not induce drug-metabolizing enzymes, as measured by antipyrine half-life.

TABLE 16. PHARMACOKINETICS AND DOSAGE ADJUSTMENT IN PEDIATRIC AND ELDERLY POPULATIONS

<table>
<tr><th>BRAND</th><th>PEDIATRIC POPULATION</th><th>ELDERLY POPULATION</th></tr>
<tr><td>LUVOX® CR
(fluvoxamine maleate)
Extended-Release Capsules

LUVOX®
(fluvoxamine maleate)
Immediate-Release Tablets</td><td>The pharmacokinetics of LUVOX® CR have not been evaluated in pediatric patients. However, the multiple-dose pharmacokinetics of immediate-release fluvoxamine maleate tablets were determined in male and female children (ages 6-11 years) (Table 2) and adolescents (ages 12-17 years) (Table 1). Steady-state plasma fluvoxamine concentrations were 2-fold to 3-fold higher in children than in adolescents. AUC and C_{max} in children were 1.5-fold to 2.7-fold higher than those in adolescents (See Table 1). As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and C_{max} compared to male children; therefore, lower doses of immediate-release fluvoxamine maleate tablets may produce therapeutic benefit (See Table 2.). No gender differences were observed in adolescents. Steady-state plasma fluvoxamine concentrations were similar in adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in these two populations (See Table 1). Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

TABLE 1. COMPARISON OF MEAN (SD) IMMEDIATE-RELEASE FLUVOXAMINE MALEATE TABLET PHARMACOKINETIC PARAMETERS BETWEEN CHILDREN, ADOLESCENTS, AND ADULTS
<table>
<tr><td>PK Parameter (body weight corrected)</td><td colspan="2">Dose=200 mg/day (100 mg bid)</td><td colspan="2">Dose=300 mg/day (150 mg bid)</td></tr>
<tr><td></td><td>Children (n=10)</td><td>Adole-scent (n=17)</td><td>Adole-scent (n=13)</td><td>Adult (n=16)</td></tr>
<tr><td>AUC 0-12 (ng·hr /mL/kg)</td><td>155.1 (160.9)</td><td>43.9 (27.9)</td><td>69.6 (46.6)</td><td>59.4 (40.9)</td></tr>
<tr><td>C_{max} (ng/mL/kg)</td><td>14.8 (14.9)</td><td>4.2 (2.6)</td><td>6.7 (4.2)</td><td>5.7 (3.9)</td></tr>
<tr><td>C_{min} (ng/mL/kg)</td><td>11.0 (11.9)</td><td>2.9 (2.0)</td><td>4.8 (3.8)</td><td>4.6 (3.2)</td></tr>
</table>
TABLE 2. COMPARISON OF MEAN (SD) IMMEDIATE-RELEASE FLUVOXAMINE MALEATE TABLET PHARMACOKINETIC PARAMETERS BETWEEN MALE AND FEMALE CHILDREN (6-11 YRS)
<table>
<tr><td rowspan="2">PK Parameter (body weight corrected)</td><td colspan="2">Dose=200 mg/day (100 mg twice daily</td></tr>
<tr><td>Male Children (n=7)</td><td>Female Children (n=3)</td></tr>
<tr><td>AUC (0-12)</td><td>95.8</td><td>293.5</td></tr>
<tr><td>(ng·hr/mL/kg)</td><td>(83.9)</td><td>(233.0)</td></tr>
<tr><td>C_{max}</td><td>9.1</td><td>28.1</td></tr>
<tr><td>(ng/mL/kg)</td><td>(7.6)</td><td>(21.1)</td></tr>
<tr><td>C_{min}</td><td>6.6</td><td>21.2</td></tr>
<tr><td>(ng/mL/kg)</td><td>(6.1)</td><td>(17.6)</td></tr>
</table></td><td>In a study using immediate-release fluvoxamine maleate tablets at 50 mg and 100 mg and comparing elderly (ages 66-73 years) and young subjects (ages 19-35 years), mean maximum plasma concentrations in the elderly were 40% higher. The multiple-dose elimination half-life of fluvoxamine was 17.4 hours and 25.9 hours in the elderly compared to 13.6 hours and 15.6 hours in the young subjects at steady state for 50 and 100 mg doses, respectively. In elderly patients administered immediate-release fluvoxamine maleate tablets, the clearance of fluvoxamine was reduced by about 50%; therefore, LUVOX® CR Capsules should be slowly titrated during initiation of therapy.</td></tr>
</table>

TABLE 16. PHARMACOKINETICS AND DOSAGE ADJUSTMENT IN PEDIATRIC AND ELDERLY POPULATIONS – CONTINUED

BRAND	PEDIATRIC POPULATION	ELDERLY POPULATION
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	No information provided	In a multiple-dose study in the elderly at daily doses of 20, 30, and 40 mg of the immediate-release formulation, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced.
Prozac® (fluoxetine hydrochloride)	Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with major depressive disorder or obsessive compulsive disorder (OCD). Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children were 2-fold higher than in adolescents (171 and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 8 to <18) diagnosed with major depressive disorder. Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.	The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

TABLE 16. PHARMACOKINETICS AND DOSAGE ADJUSTMENT IN PEDIATRIC AND ELDERLY POPULATIONS – CONTINUED

BRAND	PEDIATRIC POPULATION	ELDERLY POPULATION
ZOLOFT® (sertraline hydrochloride)	Sertraline pharmacokinetics were evaluated in a group of 61 pediatric patients (29 aged 6-12 years, 32 aged 13-17 years) with a DSM-III-R diagnosis of major depressive disorder or obsessive-compulsive disorder. Patients included both males (N=28) and females (N=33). During 42 days of chronic sertraline dosing, sertraline was titrated up to 200 mg/day and maintained at that dose for a minimum of 11 days. On the final day of sertraline 200 mg/day, the 6-12 year old group exhibited a mean sertraline AUC (0-24 hr) of 3107 ng-hr/mL, mean C_{max} of 165 ng/mL, and mean half-life of 26.2 hr. The 13-17 year old group exhibited a mean sertraline AUC (0-24 hr) of 2296 ng-hr/mL, mean C_{max} of 123 ng/mL, and mean half-life of 27.8 hr. Higher plasma levels in the 6-12 year old group were largely attributable to patients with lower body weights. No gender associated differences were observed. By comparison, a group of 22 separately studied adults between 18 and 45 years of age (11 male, 11 female) received 30 days of 200 mg/day sertraline and exhibited a mean sertraline AUC (0-24 hr) of 2570 ng-hr/mL, mean C_{max} of 142 ng/mL, and mean half-life of 27.2 hr. Relative to the adults, both the 6-12 year olds and the 13-17 year olds showed about 22% lower AUC (0-24 hr) and C_{max} values when plasma concentration was adjusted for weight. These data suggest that pediatric patients metabolize sertraline with slightly greater efficiency than adults. Nevertheless, lower doses may be advisable for pediatric patients given their lower body weights, especially in very young patients, in order to avoid excessive plasma levels.	Sertraline plasma clearance in a group of 16 (8 male, 8 female) elderly patients treated for 14 days at a dose of 100 mg/day was approximately 40% lower than in a similarly studied group of younger (25 to 32 y.o.) individuals. Steady-state, therefore, should be achieved after 2 to 3 weeks in older patients. The same study showed a decreased clearance of desmethylsertraline in older males, but not in older females.
EFFEXOR XR® (venlafaxine hydrochloride)		The pharmacokinetics of venlafaxine and O-didesmethylvenlafaxine are not substantially altered in the elderly. No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction. A population pharmacokinetic analysis of 404 venlafaxine-treated patients from two studies involving both b.i.d. and t.i.d. regimens showed that dose-normalized trough plasma levels of either venlafaxine or O-didesmethylvenlafaxine were unaltered by age or gender differences. As with any drug for the treatment of major depressive disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, or panic disorder, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

BRAND	PEDIATRIC POPULATION	ELDERLY POPULATION
Anafranil® (clomipramine hydrochloride)	Children under 15 years of age had significantly lower plasma concentration/dose ratios, compared with adults.	Younger subjects (18 to 40 years of age) tolerated clomipramine better and had significantly lower steady-state plasma concentrations, compared with subjects over 65 years of age.

TABLE 17. PHARMACOKINETICS AND DOSAGE ADJUSTMENT IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

BRAND	RENAL IMPAIRMENT	HEPATIC IMPAIRMENT
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 mL/min to 45 mL/min) after 4 weeks and 6 weeks of treatment (50 mg given twice daily, N=13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients.	A cross-study comparison (healthy subjects versus patients with hepatic dysfunction) using immediate-release fluvoxamine maleate tablets suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction.
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min. were approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}). The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals.	
Prozac® (fluoxetine hydrochloride)	In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients.	As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used.
ZOLOFT® (sertraline hydrochloride)	Sertraline is extensively metabolized and excretion of unchanged drug in urine is a minor route of elimination. In volunteers with mild to moderate (CLcr=30-60 mL/min), moderate to severe (CLcr=10-29 mL/min) or severe (receiving hemodialysis) renal impairment (N=10 each group), the pharmacokinetics and protein binding of 200 mg sertraline per day maintained for 21 days were not altered compared to age-matched volunteers (N=12) with no renal impairment. Thus sertraline multiple dose pharmacokinetics appear to be unaffected by renal impairment.	As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of sertraline. In patients with chronic mild liver impairment (N=10, 8 patients with Child-Pugh scores of 5-6 and 2 patients with Child-Pugh scores of 7-8) who received 50 mg sertraline per day maintained for 21 days, sertraline clearance was reduced, resulting in approximately 3-fold greater exposure compared to age-matched volunteers with no hepatic impairment (N=10). The exposure to desmethylsertraline was approximately 2-fold greater compared to age-matched volunteers with no hepatic impairment. There were no significant differences in plasma protein binding observed between the two groups. The effects of sertraline in patients with moderate and severe hepatic impairment have not been studied. The results suggest that the use of sertraline in patients with liver disease must be approached with caution. If sertraline is administered to patients with liver impairment, a lower or less frequent dose should be used.

TABLE 17. PHARMACOKINETICS AND DOSAGE ADJUSTMENT IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT – CONTINUED

BRAND	RENAL IMPAIRMENT	HEPATIC IMPAIRMENT
EFFEXOR XR® (venlafaxine hydrochloride)	In a renal impairment study, venlafaxine elimination half-life after oral administration was prolonged by about 50% and clearance was reduced by about 24% in renally impaired patients (GFR=10 to 70 mL/min), compared to normal subjects. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was reduced by about 57% compared to normal subjects. Similarly, O-didesmethylvenlafaxine elimination half-life was prolonged by about 40% although clearance was unchanged in patients with renal impairment (GFR=10 to 70 mL/min) compared to normal subjects. In dialysis patients, O-didesmethylvenlafaxine elimination half-life was prolonged by about 142% and clearance was reduced by about 56% compared to normal subjects. A large degree of intersubject variability was noted. Dosage adjustment is necessary in these patients	In 9 subjects with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and O-didesmethylvenlafaxine was significantly altered after oral administration of venlafaxine. Venlafaxine elimination half-life was prolonged by about 30%, and clearance decreased by about 50% in cirrhotic subjects compared to normal subjects. ODV elimination half-life was prolonged by about 60%, and clearance decreased by about 30% in cirrhotic subjects compared to normal subjects. A large degree of intersubject variability was noted. Three patients with more severe cirrhosis had a more substantial decrease in venlafaxine clearance (about 90%) compared to normal subjects. In a second study, venlafaxine was administered orally and intravenously in normal (n=21) subjects, and in Child-Pugh A (n=8) and Child-Pugh B (n=11) subjects (mildly and moderately impaired, respectively). Venlafaxine oral bioavailability was increased 2-3 fold, oral elimination half-life was approximately twice as long and oral clearance was reduced by more than half, compared to normal subjects. In hepatically impaired subjects, O-didesmethylvenlafaxine oral elimination half-life was prolonged by about 40%, while oral clearance for O-didesmethylvenlafaxine was similar to that for normal subjects. A large degree of intersubject variability was noted. Dosage adjustment is necessary in these hepatically impaired patients.
Anafranil® (clomipramine hydrochloride)	The effects of hepatic and renal impairment on the disposition of Anafranil have not been determined.	

TABLE 18. WARNINGS

BRAND	BOX WARNING SUICIDALITY & ANTIDEPRESSANT DRUGS	CLINICAL WORSENING/ SUICIDE	MAOI INTERACTION	SCREENING FOR BIPOLAR DISORDER	SEROTONIN SYNDROME
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	X	X	X	X	X
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets					
PAXIL® (paroxetine hydrochloride)	X	X	X	X	X
PAXIL® CR (paroxetine hydrochloride) controlled release					
Prozac® (fluoxetine hydrochloride)	X	X		X	X
ZOLOFT® (sertraline hydrochloride)	X	X	X	X	X
EFFEXOR XR® (venlafaxine hydrochloride)	X	X	X	X	X
Anafranil® (clomipramine hydrochloride)	X	X	X	X	

MAOI=monoamine oxidase inhibitor.

TABLE 18. WARNINGS – CONTINUED

BRAND	THIORIDAZINE INTERACTION	POTENTIAL PIMOZIDE INTERACTION	BENZODIAZEPAM, THEOPHYLLINE, AND/OR WARFARIN INTERACTIONS
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	X	X	X
LUVOX® (fluvoxamine maleate)			
PAXIL® (paroxetine hydrochloride)	X		
PAXIL® CR (paroxetine hydrochloride) controlled release			
Prozac® (fluoxetine hydrochloride)	X		
ZOLOFT® (sertraline hydrochloride)			
EFFEXOR XR® (venlafaxine hydrochloride)			
Anafranil® (clomipramine hydrochloride)			

TABLE 18. WARNINGS – CONTINUED

BRAND	SUSTAINED HYPERTENSION	MYDRIASIS	SEIZURE	RASH & POSSIBLY ALLERGIC EVENTS
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules				
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets				
PAXIL® (paroxetine hydrochloride)				
PAXIL® CR (paroxetine hydrochloride) controlled release				
Prozac® (fluoxetine hydrochloride)				X
ZOLOFT® (sertraline hydrochloride)				
EFFEXOR XR® (venlafaxine hydrochloride)	X	X		
Anafranil® (clomipramine hydrochloride)			X	

TABLE 19. GENERAL PRECAUTIONS

BRAND	ABRUPT DISCONTINUATION	ABNORMAL BLEEDING	ACTIVATION OF MANIA/ HYPOMANIA	SEIZURES	HYPONATREMIA
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	X	X	X	X	X
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets					
PAXIL® (paroxetine hydrochloride)					
PAXIL® CR (paroxetine hydrochloride) Controlled Release	X	X	X	X	X
Prozac® (fluoxetine hydrochloride)	X	X	X	X	X
ZOLOFT® (sertraline hydrochloride)	X	X	X	X	X
EFFEXOR XR® (venlafaxine hydrochloride)	X	X	X	X	X
Anafranil® (clomipramine hydrochloride)	X		X		

TABLE 19. GENERAL PRECAUTIONS – CONTINUED

BRAND	ILLNESS	ALTERED PLATELET FUNCTION / ABNORMAL LAB RESULTS	COGNITIVE / MOTOR PERFORMANCE	AKATHISIA
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	X		X	
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	X		X	X
Prozac® (fluoxetine hydrochloride)	X		X	
ZOLOFT® (sertraline hydrochloride)	X	X	X	
EFFEXOR XR® (venlafaxine hydrochloride)	X		X	
Anafranil® (clomipramine hydrochloride)	X			

TABLE 19. GENERAL PRECAUTIONS – CONTINUED

BRAND	ANXIETY/ INSOMNIA	ALTERED APPETITE/ WEIGHT	LONG ELIMINATION HALF-LIFE	WEAK URICOSURIC EFFECT
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules				
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets				
PAXIL® (paroxetine hydrochloride)				
PAXIL® CR (paroxetine hydrochloride) controlled release				
Prozac® (fluoxetine hydrochloride)	X	X	X	
ZOLOFT® (sertraline hydrochloride)		X		X
EFFEXOR XR® (venlafaxine hydrochloride)	X	X		
Anafranil® (clomipramine hydrochloride)		X		

TABLE 19. GENERAL PRECAUTIONS – CONTINUED

BRAND	HEPATIC EFFECTS	HEMATOLOGIC EFFECTS	HYPER-THERMIA	CHOLESTEROL ELEVATION	INTERSTITIAL LUNG DISEASE
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules					
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets					
PAXIL® (paroxetine hydrochloride)					
PAXIL® CR (paroxetine hydrochloride) controlled release					
Prozac® (fluoxetine hydrochloride)					
ZOLOFT® (sertraline hydrochloride)					
EFFEXOR XR® (venlafaxine hydrochloride)				X	X
Anafranil® clomipramine hydrochloride)	X	X	X		

TABLE 19. GENERAL PRECAUTIONS – CONTINUED

BRAND	SEXUAL AE	CV EFFECTS	ECT	PSYCHOSIS/CONFUSION	SURGERY
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules					
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets					
PAXIL® (paroxetine hydrochloride)					
PAXIL® CR (paroxetine hydrochloride) controlled release					
Prozac® (fluoxetine hydrochloride)					
ZOLOFT® (sertraline hydrochloride)					
EFFEXOR XR® (venlafaxine hydrochloride)					
Anafranil® clomipramine hydrochloride)	X	X	X	X	X

AE=adverse effects; CV=cardiovascular; ECT=electroconvulsive therapy.

TABLE 20. CONTRAINDICATIONS

BRAND	CONTRAINDICATIONS
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	• Co-administration with alosetron, tizanidine, thioridazine, pimozide • Use of monoamine oxidase inhibitors within 14 days of discontinuing LUVOX® CR • Hypersensitivity
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	• Concomitant use of monoamine oxidase inhibitors, thioridazine, pimozide • Hypersensitivity
Prozac® (fluoxetine hydrochloride) ZOLOFT® (sertraline hydrochloride)	• Thioridazine • Monoamine oxidase inhibitors, pimozide • Concomitant use of monoamine oxidase inhibitors, pimozide, Antabuse (oral concentration formula of ZOLOFT only)
EFFEXOR XR® (venlafaxine hydrochloride)	• Concomitant use of monoamine oxidase inhibitors • Hypersensitivity
Anafranil® (clomipramine hydrochloride)	• Within 14 days of use of monoamine oxidase inhibitors • During the acute recovery period following myocardial infarction • Hypersensitivity

TABLE 21. DRUG INTERACTIONS

BRAND	DRUG INTERACTIONS
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	**Drugs that Inhibit or are Metabolized by Cytochrome P450 Isoenzymes** **CNS Active Drugs** Antipsychotics MAOIs Benzodiazepines Alcohol Carbamazepine Clozapine Lithium Lorazepam Methadone Ramelteon Serotonergic drugs Sumatriptan Tacrine Thioridazine Triptans Tizanidine Tricyclic Antidepressants Tryptophan **Drugs that Interfere with Hemostasis (e.g., NSAIDS, Aspirin, Warfarin)** **Other Drugs** Theophylline Warfarin Alosetron Digoxin Diltiazem Beta-blockers
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	**Drugs Affecting Hepatic Metabolism** **Drugs Metabolized by CYP2D6** **Drugs Metabolized by Cytochrome CYP3A4** **Drugs Highly Bound to Plasma Proteins** **Drugs that Interfere with Hemostasis (e.g., NSAIDS, Aspirin, Warfarin)** **CNS Active Drugs** Alcohol Diazepam Linezolid Lithium MAOIs Phenobarbital Phenytoin Pimozide Procyclidine Serotonergic Drugs St. John's Wort Thioridazine Tramadol Tricyclic Antidepressants Triptans Tryptophan **Other Drugs** Beta-blockers Cimetidine Digoxin Fosamprenavir/Ritonavir Theophylline Warfarin

TABLE 21. DRUG INTERACTIONS – CONTINUED

BRAND	DRUG INTERACTIONS
Prozac® (fluoxetine hydrochloride)	**Drugs Metabolized by CYP2D6** **Drugs Metabolized by Cytochrome CYP3A4** **Drugs Tightly Bound to Plasma Proteins** **Drugs that Interfere with Hemostasis (e.g., NSAIDS, Aspirin, Warfarin)** **CNS Active Drugs** Antipsychotics Anticonvulsants Benzodiazepines Lithium MAOIs Serotonergic drugs Sumatriptan Tricyclic antidepressants Triptans Tryptophan **Other Drugs** Warfarin
ZOLOFT® (sertraline hydrochloride)	**Drugs Tightly Bound to Plasma Proteins** **Drugs Metabolized by CYP2D6** **Drugs Metabolized by Cytochrome CYP3A4** **Drugs that Induce Hepatic Microsomal Enzymes** **Drugs that Interfere with Hemostasis (e.g., NSAIDS, Aspirin, Warfarin)** **CNS Active Drugs** Alcohol Diazepam Lithium MAOIs Phenytoin Pimozide Serotonergic drugs Sumatriptan Tricyclic antidepressants Triptans **Other Drugs** Atenolol Digoxin Cimetidine Hypoglycemic drugs
EFFEXOR XR® (venlafaxine hydrochloride)	**CNS Active Drugs** Alcohol Diazepam Haliperidol Lithium MAOI Serotonergic Drugs Triptans **Drugs Highly Bound to Plasma Proteins** **Drugs Metabolized by Cytochrome P450** Imiprazine Risperidone Indinavir **Drugs that Inhibit Cytochrome P450** CYP2D6 Inhibitors Ketoconazole **Other Drugs** Cimetidine

TABLE 21. DRUG INTERACTIONS – CONTINUED

BRAND	DRUG INTERACTIONS
Anafranil® (clomipramine hydrochloride)	**Drugs Metabolized by CYP2D6** **CNS Active Drugs** Anticholinergic drugs Antipsychotic drugs MAOIs Phenobarbital Tricyclic antidepressants **Hepatic Enzyme Inhibitors** **Hepatic Enzyme Inducers** **Other Drugs** Digoxin Warfarin)

CNS=central nervous system; MAOI=monoamine oxidase inhibitor; NSAIDS=nonsteroidal anti-inflammatory drugs

TABLE 22. FERTILITY, PREGNANCY, AND NURSING MOTHERS

BRAND	IMPAIRMENT OF FERTILITY	PREGNANCY CATEGORY	NURSING MOTHERS
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	In a study in which male and female rats were administered fluvoxamine (60 mg/kg, 120 mg/kg, or 240 mg/kg) orally prior to and during mating and gestation, fertility was impaired at doses of 120 mg/kg or greater, as evidenced by increased latency to mating, decreased sperm count, decreased epididymal weight, and decreased pregnancy rate. In addition, the numbers of implantations and embryos were decreased at the highest dose. The no effect dose for fertility impairment was 60 mg/kg (approximately 2 times the maximum recommended human dose [MRHD] on a mg/m^2 basis).	C	Fluvoxamine is secreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants from LUVOX® CR and LUVOX® IR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for MDD, SAD, GAD, or PTSD and 2.4 times the MRHD for OCD on a mg/m^2 basis for PAXIL, and approximately twice the MRHD on a mg/m^2 basis for PAXIL CR. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for MDD, SAD, and GAD; 8.2 and 4.1 times the MHRD for OCD and PD for PAXIL and approximately 8 and 4 times the MRHD for PAXIL CR on a mg/m^2 basis).	D	Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when PAXIL is administered to a nursing woman.
Prozac® (fluoxetine hydrochloride)	Two fertility studies conducted in adult rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility (*see* Pediatric Use).	C	Because Prozac is excreted in human milk, nursing while on Prozac is not recommended. In one breast-milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

TABLE 22. FERTILITY, PREGNANCY, AND NURSING MOTHERS – CONTINUED

BRAND	IMPAIRMENT OF FERTILITY	PREGNANCY CATEGORY	NURSING MOTHERS
ZOLOFT® (sertraline hydrochloride)	A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum recommended human dose on a mg/m^2 basis).	C	It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman.
EFFEXOR XR® (venlafaxine hydrochloride).	Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 2 times the maximum recommended human dose on a mg/m^2 basis.	C	Venlafaxine and O-didesmethylvenlafaxine have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Anafranil® (clomipramine hydrochloride)	In reproduction studies, no effects on fertility were found in rats given up to 24 mg/kg, which is 6 times, and approximately equal to, the MRHD on a mg/kg and mg/m^2 basis, respectively.	C	Anafranil® (clomipramine hydrochloride capsules USP) has been found in human milk. Because of the potential for adverse reactions, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

TABLE 23. USE IN PEDIATRIC POPULATIONS

BRAND	PEDIATRIC USE
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	LUVOX® CR Capsules have not been evaluated in pediatric patients. Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established. Anyone considering the use of LUVOX® CR Capsules in a child or adolescent must balance the potential risks with the clinical need. The efficacy of fluvoxamine maleate administered as immediate-release tablets for the treatment of OCD, was demonstrated in a 10-week multicenter placebo-controlled study with 120 outpatients ages 8-17 years. In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment for up to another 1 to 3 years, equivalent to 94 patient years. The adverse event profile observed in that study was generally similar to that observed in adult studies with immediate-release fluvoxamine maleate tablets. Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	The risks, if any, that may be associated with fluvoxamine's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents derives from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long-term fluvoxamine use on the growth, cognitive behavioral development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of fluvoxamine to have adverse effects in chronic use.
PAXIL® (paroxetine hydrochloride)	Safety and effectiveness in the pediatric population have not been established. Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with PAXIL, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of PAXIL in a child or adolescent must balance the potential risks with the clinical need.
PAXIL® CR (paroxetine hydrochloride) controlled release	In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with immediate-release PAXIL and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation. Events reported upon discontinuation of treatment with immediate-release PAXIL in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received immediate-release PAXIL and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain.

TABLE 23. USE IN PEDIATRIC POPULATIONS – CONTINUED

BRAND	PEDIATRIC USE
Prozac® (fluoxetine hydrochloride)	The efficacy of Prozac for the treatment of major depressive disorder was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤18. The efficacy of Prozac for the treatment of OCD was demonstrated in one 13-week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to <18. The safety and effectiveness in pediatric patients <8 years of age in major depressive disorder and <7 years of age in OCD have not been established. Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤18) with major depressive disorder or OCD. The acute adverse event profiles observed in the 3 studies (N=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse event profile observed in the 19-week major depressive disorder study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine. Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients. Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the acute phases of the three studies combined. Consequently, regular monitoring for the occurrence of mania/hypomania is recommended. As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height (p=0.004) and 1.1 kg less in weight (p=0.008) than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development, and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine. Significant toxicity, including myotoxicity, long-term neurobehavioral and reproductive toxicity, and impaired bone development, has been observed following exposure of juvenile animals to fluoxetine. Some of these effects occurred at clinically relevant exposures. In a study in which fluoxetine (3, 10, or 30 mg/kg) was orally administered to young rats from weaning (Postnatal Day 21) through adulthood (Day 90), male and female sexual development was delayed at all doses, and growth (body weight gain, femur length) was decreased during the dosing period in animals receiving the highest dose. At the end of the treatment period, serum levels of creatine kinase (marker of muscle damage) were increased at the intermediate and high doses, and abnormal muscle and reproductive organ histopathology (skeletal muscle degeneration and necrosis, testicular degeneration and necrosis, epididymal vacuolation and hypospermia) was observed at the high dose. When animals were evaluated after a recovery period (up to 11 weeks after cessation of dosing), neurobehavioral abnormalities (decreased reactivity at all doses and learning deficit at the high dose) and reproductive functional impairment (decreased mating at all doses and impaired fertility at the high dose) were seen; in addition, testicular and epididymal microscopic lesions and decreased sperm concentrations were found in the high dose group, indicating that the reproductive organ effects seen at the end of treatment were irreversible. The reversibility of fluoxetine-induced muscle damage was not assessed. Adverse effects similar to those observed in rats treated with fluoxetine during the juvenile period have not been reported after administration of fluoxetine to adult animals. Plasma exposures (AUC) to fluoxetine in juvenile rats receiving the low, intermediate, and high dose in this study were approximately 0.1-0.2, 1-2, and 5-10 times, respectively, the average exposure in pediatric patients receiving the maximum recommended dose (MRD) of 20 mg/day. Rat exposures to the major metabolite, norfluoxetine, were approximately 0.3-0.8, 1-8, and 3-20 times, respectively, pediatric exposure at the MRD. A specific effect of fluoxetine on bone development has been reported in mice treated with fluoxetine during the juvenile period. When mice were treated with fluoxetine (5 or 20 mg/kg, intraperitoneal) for 4 weeks starting at 4 weeks of age, bone formation was reduced resulting in decreased bone mineral content and density. These doses did not affect overall growth (body weight gain or femoral length). The doses administered to juvenile mice in this study are approximately 0.5 and 2 times the MRD for pediatric patients on a body surface area (mg/m^2) basis.

TABLE 23. USE IN PEDIATRIC POPULATIONS – CONTINUED

BRAND	PEDIATRIC USE
	In another mouse study, administration of fluoxetine (10 mg/kg intraperitoneal) during early postnatal development (Postnatal Days 4 to 21) produced abnormal emotional behaviors (decreased exploratory behavior in elevated plus-maze, increased shock avoidance latency) in adulthood (12 weeks of age). The dose used in this study is approximately equal to the pediatric MRD on a mg/m^2 basis. Because of the early dosing period in this study, the significance of these findings to the approved pediatric use in humans is uncertain. Prozac is approved for use in pediatric patients with MDD and OCD. Anyone considering the use of Prozac in a child or adolescent must balance the potential risks with the clinical need.
ZOLOFT® sertraline hydrochloride)	The efficacy of ZOLOFT for the treatment of obsessive-compulsive disorder was demonstrated in a 12-week, multicenter, placebo-controlled study with 187 outpatients ages 6-17. Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established. Two placebo controlled trials (n=373) in pediatric patients with MDD have been conducted with Zoloft, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Zoloft in a child or adolescent must balance the potential risks with the clinical need. The safety of ZOLOFT use in children and adolescents with OCD, ages 6-18, was evaluated in a 12-week, multicenter, placebo-controlled study with 187 outpatients, ages 6-17, and in a flexible dose, 52-week open extension study of 137 patients, ages 6-18, who had completed the initial 12-week, double-blind, placebo-controlled study. ZOLOFT was administered at doses of either 25 mg/day (children, ages 6-12) or 50 mg/day (adolescents, ages 13-18) and then titrated in weekly 25 mg/day or 50 mg/day increments, respectively, to a maximum dose of 200 mg/day based upon clinical response. The mean dose for completers was 157 mg/day. In the acute 12-week pediatric study and in the 52-week study, ZOLOFT had an adverse event profile generally similar to that observed in adults. Sertraline pharmacokinetics were evaluated in 61 pediatric patients between 6 and 17 years of age with MDD or OCD and revealed similar drug exposures to those of adults when plasma concentration was adjusted for weight. Approximately 600 patients with MDD or OCD between 6 and 17 years of age have received ZOLOFT in clinical trials, both controlled and uncontrolled. The adverse event profile observed in these patients was generally similar to that observed in adult studies with ZOLOFT. As with other SSRIs, decreased appetite and weight loss have been observed in association with the use of ZOLOFT. In a pooled analysis of two 10-week, double-blind, placebo-controlled, flexible dose (50-200 mg) outpatient trials for MDD (n=373), there was a difference in weight change between sertraline and placebo of roughly 1 kilogram, for both children (ages 6-11) and adolescents (ages 12-17), in both cases representing a slight weight loss for sertraline compared to a slight gain for placebo. At baseline the mean weight for children was 39.0 kg for sertraline and 38.5 kg for placebo. At baseline the mean weight for adolescents was 61.4 kg for sertraline and 62.5 kg for placebo. There was a bigger difference between sertraline and placebo in the proportion of outliers for clinically important weight loss in children than in adolescents. For children, about 7% had a weight loss >7% of body weight compared to none of the placebo patients; for adolescents, about 2% had a weight loss >7% of body weight compared to about 1% of the placebo patients. A subset of these patients who completed the randomized controlled trials (sertraline n=99, placebo n=122) were continued into a 24-week, flexible-dose, open-label, extension study. A mean weight loss of approximately 0.5 kg was seen during the first 8 weeks of treatment for subjects with first exposure to sertraline during the open-label extension study, similar to mean weight loss observed among sertraline treated subjects during the first 8 weeks of the randomized controlled trials. The subjects continuing in the open-label study began gaining weight compared to baseline by week 12 of sertraline treatment. Those subjects who completed 34 weeks of sertraline treatment (10 weeks in a placebo controlled trial + 24 weeks open label, n=68) had weight gain that was similar to that expected using data from age-adjusted peers. Regular monitoring of weight and growth is recommended if treatment of a pediatric patient with an SSRI is to be continued long term. Safety and effectiveness in pediatric patients below the age of 6 have not been established. The risks, if any, that may be associated with ZOLOFT's use beyond 1 year in children and adolescents with OCD or MDD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that sertraline is safe for use in children and adolescents derives from clinical studies that were 10 to 52 weeks in duration and from the extrapolation of experience gained with adult patients. In particular, there are no studies that

TABLE 23. USE IN PEDIATRIC POPULATIONS – CONTINUED

BRAND	PEDIATRIC USE
	directly evaluate the effects of long-term sertraline use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that sertraline possesses a capacity to adversely affect growth, development, or maturation, the absence of such findings is not compelling evidence of the absence of the potential of sertraline to have adverse effects in chronic use.
EFFEXOR XR® (venlafaxine hydrochloride)	Safety and effectiveness in the pediatric population have not been established. Two placebo-controlled trials in 766 pediatric patients with MDD and two placebo-controlled trials in 793 pediatric patients with GAD have been conducted with EFFEXOR XR, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Effexor XR in a child or adolescent must balance the potential risks with the clinical need. Although no studies have been designed to primarily assess Effexor XR's impact on the growth, development, and maturation of children and adolescents, the studies that have been done suggest that Effexor XR may adversely affect weight and height. Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if it is to be continued long term. The safety of Effexor XR treatment for pediatric patients has not been systematically assessed for chronic treatment longer than six months in duration. In the studies conducted in pediatric patients (ages 6-17), the occurrence of blood pressure and cholesterol increases considered to be clinically relevant in pediatric patients was similar to that observed in adult patients. Consequently, the precautions for adults apply to pediatric patients.
Anafranil® (clomipramine hydrochloride)	Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established. Anyone considering the use of Anafranil in a child or adolescent must balance the potential risks with the clinical need. In a controlled clinical trial in children and adolescents (10 to 17 years of age), 46 outpatients received Anafranil for up to 8 weeks. In addition, 150 adolescent patients have received Anafranil in open-label protocols for periods of several months to several years. Of the 196 adolescents studied, 50 were 13 years of age or less and 146 were 14 to 17 years of age. The adverse reaction profile in this age group is similar to that observed in adults. The risks, if any, that may be associated with Anafranil's extended use in children and adolescents with OCD have not been systematically assessed. The evidence supporting the conclusion that Anafranil is safe for use in children and adolescents is derived from relatively short-term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long term Anafranil use on the growth, development, and maturation of children and adolescents. Although there is no evidence to suggest that Anafranil adversely affects growth, development, or maturation, the absence of such findings is not adequate to rule out a potential for such effects in chronic use. The safety and effectiveness in pediatric patients below the age of 10 have not been established. Therefore, specific recommendations cannot be made for the use of Anafranil in pediatric patients under the age of 10.

TABLE 24 . USE IN GERIATRIC POPULATIONS

BRAND	GERIATRIC USE
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	Approximately 230 patients and 5 patients participating in controlled premarketing studies with immediate-release fluvoxamine maleate tablets and LUVOX® CR Capsules, respectively, were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. However, SSRIs and SNRIs, including LUVOX® CR Capsules, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at increased risk for this adverse event. Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients, and greater sensitivity of some older individuals also cannot be ruled out. Consequently, immediate-release fluvoxamine maleate tablets and LUVOX® CR Capsules should be slowly titrated during initiation of therapy.
PAXIL® (paroxetine hydrochloride) PAXIL® CR (paroxetine hydrochloride) controlled release	SSRIs and SNRIs, including PAXIL, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event. In worldwide premarketing clinical trials, 17% of paroxetine-treated patients (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients. In a controlled study focusing specifically on elderly patients with major depressive disorder, PAXIL CR was demonstrated to be safe and effective in the treatment of elderly patients (>60 years) with major depressive disorder.
Prozac® (fluoxetine hydrochloride)	US fluoxetine clinical trials as of May 8, 1995 (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. The efficacy in geriatric patients has been established. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients.
ZOLOFT® (sertraline hydrochloride)	U.S. geriatric clinical studies of ZOLOFT in MDD included 663 ZOLOFT-treated subjects ≥ 65 years of age, of those, 180 were ≥75 years of age. No overall differences in the pattern of adverse reactions were observed in the geriatric clinical trial subjects relative to those reported in younger subjects, and other reported experience has not identified differences in safety patterns between the elderly and younger subjects. As with all medications, greater sensitivity of some older individuals cannot be ruled out. There were 947 subjects in placebo-controlled geriatric clinical studies of ZOLOFT in MDD. No overall differences in the pattern of efficacy were observed in the geriatric clinical trial subjects relative to those reported in younger subjects. Other Adverse Events in Geriatric Patients. In 354 geriatric subjects treated with ZOLOFT in placebo-controlled trials, the overall profile of adverse events was generally similar to that seen in younger patients. Urinary tract infection was reported at an incidence of at least 2% and at a rate greater than placebo in placebo-controlled trials. As with other SSRIs, ZOLOFT has been associated with cases of clinically significant hyponatremia in elderly patients.
EFFEXOR XR® (venlafaxine hydrochloride)	Approximately 4% (14/357), 6% (77/1381), 2% (6/277), and 2% (16/1001) of Effexor XR-treated patients in placebo-controlled premarketing major depressive disorder, GAD, Social Anxiety Disorder trials, and panic disorder trials, respectively, were 65 years of age or over. Of 2,897 Effexor-treated patients in premarketing phase major depressive disorder studies, 12% (357) were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients, and other reported clinical experience generally has not identified differences in response between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Effexor XR have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event. The pharmacokinetics of venlafaxine and O-didesmethylvenlafaxine are not substantially altered in the elderly. No dose adjustment is recommended for the elderly on the basis of age alone, although other clinical circumstances, some of which may be more common in the elderly, such as renal or hepatic impairment, may warrant a dose reduction.

TABLE 24 . USE IN GERIATRIC POPULATIONS – CONTINUED

BRAND	GERIATRIC USE
Anafranil® (clomipramine hydrochloride)	Clinical studies of Anafranil did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects; 152 patients at least 60 years of age participating in various U.S. clinical trials received Anafranil for periods of several months to several years. No unusual age-related adverse events were identified in this population. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

TABLE 25. ADVERSE EVENTS

BRAND	ADVERSE EVENTS
LUVOX® CR (fluvoxamine maleate) Extended-Release Capsules	**Associated with Discontinuation of Treatment** Of the 279 patients with social anxiety disorder and 124 patients with OCD treated with LUVOX® CR Capsules in controlled clinical trials, 26% and 19% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) are provided in Table 4.

TABLE 4. ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN SOCIAL ANXIETY DISORDER AND OCD POPULATIONS[1]

	PERCENTAGE OF PATIENTS			
	SOCIAL ANXIETY DISORDER		OCD	
BODY SYSTEM/ ADVERSE EVENT	LUVOX® CR	PLACEBO	LUVOX® CR	PLACEBO
BODY AS A WHOLE				
Asthenia	4	<1	2	0
Headache	3	<1	–	–
Abdominal Pain	1	0	–	–
Pain	–	–	2	0
DIGESTIVE				
Nausea	8	<1	6	0
Diarrhea	3	0	2	0
Anorexia[1]	2	0	–	–
Dyspepsia	–	–	2	0
NERVOUS SYSTEM				
Insomnia	5	<1	5	2
Somnolence	5	<1	4	0
Anxiety	4	<1	2	<1
Dizziness	4	0	3	0
Abnormal Thinking	2	<1	–	–
Nervousness	2	<1	–	–
Depression	1	0	–	–
Agitation	1	0	–	–
Paresthesia	1	0	–	–
Tremor	1	0	–	–
SKIN AND APPENDAGES				
Sweating	1	0	–	–

[1] Includes, but is not limited to, loss of appetite and decreased appetite.

Incidence in Controlled Trials

Commonly Observed Adverse Events: LUVOX® CR Capsules have been studied in two controlled trials of social anxiety disorder (N=279) and one trial of OCD (N=124). In general, adverse event rates were similar in the two data sets as well as in a study of pediatric patients with OCD treated with immediate-release fluvoxamine maleate tablets. The most commonly observed adverse events associated with the use of LUVOX® CR Capsules and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) for patients in SAD and in OCD derived from Table 5 were: *abnormal ejaculation, anorexia, anorgasmia asthenia, diarrhea, nausea, somnolence, sweating and tremor*. In addition, the following events occurred in the SAD population: *dyspepsia, dizziness, insomnia, and yawning*. In the OCD population, the following additional events occurred: *accidental injury, anxiety, decreased libido, myalgia, pharyngitis, and vomiting*. In a study evaluating immediate-release fluvoxamine maleate tablets in pediatric patients with OCD, the following additional events were identified using the above rule: *agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash.*

Adverse Events Occurring at an Incidence of 2%: Table 5 enumerates adverse events that occurred in adults at a frequency of 2% or more, and were more frequent than in the placebo group, among patients treated with LUVOX® CR Capsules in two short-term, placebo-controlled social anxiety disorder trials (12 week) and one short-term placebo-controlled OCD trial (12 week) and in which patients were dosed once-a-day in a range of 100 mg/day to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

during their treatment. Reported adverse events were classified using a COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing health care provider with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

TABLE 5 TREATMENT-EMERGENT ADVERSE EVENT RATES BY BODY SYSTEM IN ADULT SAD AND OCD POPULATIONS[1]

	PERCENTAGE OF PATIENTS REPORTING EVENT			
	SOCIAL ANXIETY DISORDER		OCD	
BODY SYSTEM/ ADVERSE EVENT	LUVOX® CR N=279	PLACEBO N=276	LUVOX® CR N=124	PLACEBO N=124
BODY AS A WHOLE				
Headache	35	30	32	31
Asthenia	24	10	26	8
Pain[2]	–	–	10	8
Abdominal Pain	5	4	–	–
Accidental Injury	–	–	5	3
Chest Pain	3	1	–	–
Viral Infection	–	–	2	<1
CARDIOVASCULAR				
Palpitation	3	1	–	–
Vasodilatation	2	<1	–	–
Hypertension	–	–	2	<1
DIGESTIVE SYSTEM				
Nausea	39	11	34	13
Diarrhea	14	5	18	8
Anorexia[3]	14	1	13	5
Dyspepsia	10	4	8	5
Constipation	6	5	4	<1
Vomiting	–	–	6	2
Tooth Disorder	–	–	2	<1
Liver Function Test Abnormal	2	<1	–	–
Gingivitis	–	–	2	0
HEMIC AND LYMPHATIC				
Ecchymosis	–	–	4	2
METABOLIC AND NUTRITIONAL DISORDERS				
Weight Loss	–	–	2	<1
MUSCULOSKELETAL				
Myalgia	–	–	5	2
NERVOUS SYSTEM				
Insomnia	32	13	35	20
Somnolence	26	9	27	11
Dizziness	15	7	12	10
Dry Mouth	11	8	10	9
Nervousness	10	9	–	–

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

TABLE 5 TREATMENT-EMERGENT ADVERSE EVENT RATES BY BODY SYSTEM IN ADULT SAD AND OCD POPULATIONS – CONTINUED[1]

	SOCIAL ANXIETY DISORDER		OCD	
BODY SYSTEM/ ADVERSE EVENT	LUVOX® CR N=279	PLACEBO N=276	LUVOX® CR N=124	PLACEBO N=124
Libido Decreased	6	4	6	2
Male	8	6	10	5
Female	4	3	4	1
Anxiety	8	5	6	2
Tremor	8	<1	6	0
Abnormal Thinking	3	2	3	<1
Abnormal Dreams	3	2	–	–
Agitation	3	<1	2	<1
Hypertonia	2	1	–	–
Apathy	–	–	3	0
Paresthesia	3	2	–	–
Neurosis	–	–	2	<1
Twitching	–	–	2	0
RESPIRATORY SYSTEM				
Pharyngitis	–	–	6	<1
Yawn	5	<1	2	0
Laryngitis	–	–	3	0
Bronchitis	2	1	–	–
Epistaxis	–	–	2	0
SKIN				
Sweating	6	2	7	<1
Acne	–	–	2	0
SPECIAL SENSES				
Taste Perversion	2	<1	2	<1
Amblyopia	–	–	2	<1
UROGENITAL				
Abnormal Ejaculation	11	2	10	0
Anorgasmia	5	1	5	0
Male	4	2	4	0
Female	5	0	5	0
Menorrhagia	–	–	3	0
Sexual Function Abnormal	3	<1	2	<1
Male	2	1	4	3
Female	3	0	0	0
Urinary Tract Infection	2	<1	–	–
Polyuria	–	–	2	<1

[1] Events for which fluvoxamine maleate incidence was equal to or less than placebo include the following for SAD patients: abdominal pain, accidental injury, back pain, flu syndrome, infection, pain, flatulence, pharyngitis, rhinitis, rash, and dysmenorrhea. In OCD patients the following events were seen: abdominal pain, flu syndrome, infection, palpitation, flatulence, increased appetite, weight gain, abnormal dreams, amnesia, hypertonia, nervousness, paresthesia, increased cough, dyspnea, rhinitis, and ear pain.

[2] Term includes body aches/pains, dental pain, pain from surgery, unspecified pain, and general pain secondary to injuries (sprains, fractures).

[3] Includes, but is not limited to, loss of appetite and decreased appetite.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Other Adverse Events in OCD Pediatric Population
In pediatric patients (N=57) treated with immediate-release fluvoxamine maleate tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 5. However, the following adverse events, not appearing in Table 5, were reported in two or more of the pediatric patients and were more frequent with immediate-release fluvoxamine maleate tablets than with placebo: cough increase, dysmenorrhea, emotional lability, fever, flatulence, flu syndrome, hyperkinesia, infection, manic reaction, rash, rhinitis, and sinusitis.

Male and Female Sexual Dysfunction with SSRIs
Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder and with aging, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and health care providers may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

Table 6 displays the incidence of sexual side effects reported by at least 2% of patients taking LUVOX® CR capsules in placebo-controlled trials of SAD and OCD.

TABLE 6. PERCENTAGE OF PATIENTS REPORTING SEXUAL ADVERSE EVENTS IN PLACEBO-CONTROLLED TRIALS

ADVERSE EVENT	LUVOX® CR N=403	Placebo N=400
Abnormal Ejaculation	11	2
Anorgasmia		
Male	4	1
Female	5	0
Impotence	2	3
Libido Decreased		
Male	8	5
Female	4	2
Sexual Function Abnormal		
Male	3	5
Female	2	0

Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, health care providers should routinely inquire about such possible side effects.

Weight and Vital Sign Changes
No statistically significant differences in weight gain or loss were found between patients treated with LUVOX® CR Capsules or placebo. Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX® CR Capsules versus placebo groups in separate short-term trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various measures of vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes
Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX® CR Capsules versus placebo groups in separate short-term trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes
Comparisons of immediate-release fluvoxamine maleate tablets or LUVOX® CR Capsules and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	between fluvoxamine maleate and placebo.
	Other Events Observed During the Premarketing Evaluation of Fluvoxamine During premarketing clinical trials conducted in North America and Europe, multiple doses of immediate-release fluvoxamine maleate tablets were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standard event categories. In the tabulations which follow, a COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 2, which tabulates incidence rates of common adverse experiences in placebo-controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring between 1/100 and 1/1000 patients; and rare adverse events are those occurring in less than 1/1000 patients. ***Body as a Whole:*** **Frequent:** malaise; **Infrequent:** allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; **Rare:** cyst, pelvic pain, sudden death. ***Cardiovascular System:*** **Frequent:** hypertension, hypotension, syncope; **Infrequent:** angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes; **Rare:** AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles. ***Digestive System:*** **Frequent:** elevated liver transaminases; **Infrequent:** colitis, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, glossitis, hemorrhoids, melena, rectal hemorrhage, stomatitis; **Rare:** biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice. ***Endocrine System:*** **Infrequent:** hypothyroidism; Rare: goiter. ***Hemic and Lymphatic Systems:*** **Infrequent:** anemia, leukocytosis, lymphadenopathy, thrombocytopenia; **Rare:** leukopenia, purpura. ***Metabolic and Nutritional Systems:*** **Frequent:** edema, weight gain; **Infrequent:** dehydration, hypercholesterolemia; **Rare:** diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased. ***Musculoskeletal System:*** **Infrequent:** arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis; **Rare:** arthrosis, myopathy, pathological fracture. ***Nervous System:*** **Frequent:** amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction; **Infrequent:** agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; **Rare:** akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome. ***Respiratory System:*** **Frequent:** cough increased, sinusitis; Infrequent: asthma, bronchitis, hoarseness, hyperventilation; **Rare:** apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia. ***Skin:*** **Infrequent:** alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	discoloration, urticaria. ***Special Senses:*** **Infrequent:** accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** corneal ulcer, retinal detachment. ***Urogenital System*****: Infrequent:** anuria, breast pain, cystitis, delayed menstruation[1], dysuria, female lactation[1], hematuria, menopause[1], metrorrhagia[1], nocturia, premenstrual syndrome[1], urinary incontinence, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginitis[1]; **Rare:** kidney calculus, hematospermia[2], oliguria. [1] Based on the number of females. [2] Based on the number of males. **Postmarketing Reports** Voluntary reports of adverse events in patients taking fluvoxamine maleate immediate-release tablets that have been received since market introduction and are of unknown causal relationship to fluvoxamine use include: acute renal failure, agranulocytosis, amenorrhea, anaphylactic reaction, angioedema, aplastic anemia, bullous eruption, Henoch-Schoenlein purpura, hepatitis, hyponatremia, ileus, laryngismus, neuropathy, pancreatitis, porphyria, priapism, serotonin syndrome, severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, and ventricular tachycardia (including torsades de pointes).

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
LUVOX® (fluvoxamine maleate) Immediate-Release Tablets	**Adverse Reactions** **Associated with Discontinuation of Treatment** Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

TABLE 1: ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN DEPRESSION AND OCD POPULATIONS

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS	
	FLUVOXAMINE	PLACEBO
BODY AS A WHOLE		
Headache	3%	1%
Asthenia	2%	<1%
Abdominal Pain	1%	0%
DIGESTIVE		
Nausea	9%	1%
Diarrhea	1%	<1%
Vomiting	2%	<1%
Anorexia	1%	<1%
Dyspepsia	1%	<1%
NERVOUS SYSTEM		
Insomnia	4%	1%
Somnolence	4%	<1%
Nervousness	2%	<1%
Agitation	2%	<1%
Dizziness	2%	<1%
Anxiety	1%	<1%
Dry Mouth	1%	<1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: Fluvoxamine maleate has been studied in 10-week short-term controlled trials of OCD (N=320) and depression (N=1350). In general, adverse event rates were similar in the two data sets as well as in the pediatric OCD study. The most commonly observed adverse events associated with the use of fluvoxamine and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) derived from Table 2 were: *somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia, and sweating.* In a pool of two studies involving only patients with OCD, the following additional events were identified using the above rule: *dry mouth, decreased libido, urinary frequency, anorgasmia, rhinitis, and taste perversion*. In a study of pediatric patients with OCD, the following additional events were identified using the above rule: *agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash.*

Adverse Events Occurring at an Incidence of 1%: Table 2 enumerates adverse events that occurred in adults at a frequency of 1% or more, and were more frequent than in the placebo group, among patients treated with fluvoxamine maleate in two short-term placebo-controlled OCD trials (10 week) and depression trials (6 week) in which patients were dosed in a range of generally 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

TABLE 2: TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES BY BODY SYSTEM IN ADULT OCD AND DEPRESSION POPULATIONS COMBINED[1]

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS REPORTING EVENTS	
	FLUVOXAMINE (N=892)	PLACEBO (N=778)
BODY AS A WHOLE		
Headache	22%	20%
Asthenia	14%	6%
Flu Syndrome	3%	2%
Chills	2%	1%
CARDIOVASCULAR		
Palpitations	3%	2%
DIGESTIVE SYSTEM		
Nausea	40%	14%
Diarrhea	11%	7%
Constipation	10%	8%
Anorexia	6%	2%
Dyspepsia	10%	5%
Vomiting	5%	2%
Flatulence	4%	3%
Tooth Disorder[2]	3%	1%
Dysphagia	2%	1%
NERVOUS SYSTEM		
Somnolence	22%	8%
Insomnia	21%	10%
Dry Mouth	14%	10%
Nervousness	12%	5%
Agitation	2%	1%
Dizziness	11%	6%
Tremor	5%	1%
Anxiety	5%	3%
Vasodilation[3]	3%	1%
Hypertonia	2%	1%
Decreased Libido	2%	1%
Depression	2%	1%
CNS Stimulation	2%	1%
RESPIRATORY SYSTEM		
Upper Respiratory Infection	9%	5%
Dyspnea	2%	1%
Yawn	2%	0%
SKIN		
Sweating	7%	3%
SPECIAL SENSES		
Taste Perversion	3%	1%
Amblyopia[4]	3%	2%
UROGENITAL		
Abnormal Ejaculation[5,6]	8%	1%
Urinary Frequency	3%	2%
Impotence[6]	2%	1%
Anorgasmia	2%	0%
Urinary Retention	1%	0%

[1] Reactions for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above.
[2] Includes "toothache," "tooth extraction and abscess," and "caries."
[3] Mostly feeling warm, hot, or flushed.
[4] Mostly "blurred vision."
[5] Mostly "delayed ejaculation."
[6] Incidence based on number of male patients.

Adverse Reactions in OCD Placebo Controlled Studies Which are Markedly Different (defined as at least a two-fold difference) in Rate from the Pooled Reaction Rates in OCD and Depression Placebo Controlled Studies: The events in OCD studies with a two-fold decrease in rate compared to event rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

The events in OCD studies with a two-fold increase in rate compared to event rates in OCD and depression studies were: *asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, infection, rhinitis, anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia,* and *urinary retention.* These events are listed in order of decreasing rates in the OCD trials.

Other Adverse Events in OCD Pediatric Population
In pediatric patients (N=57) treated with fluvoxamine maleate, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse events, not appearing in Table 2, were reported in two or more of the pediatric patients and were more frequent with fluvoxamine maleate than with placebo: abnormal thinking, cough increase, dysmenorrhea, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight decrease.

Male and Female Sexual Dysfunction with SSRIs
Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder and with aging, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. The table below displays the incidence of sexual side effects reported by at least 2% of patients taking fluvoxamine in placebo controlled trials in depression and OCD.

TABLE 3. PERCENTAGE OF PATIENTS REPORTING SEXUAL ADVERSE EVENTS IN ADULT PLACEBO-CONTROLLED TRIALS IN OCD AND DEPRESSION

	Fluvoxamine N=892	Placebo N=778
Abnormal Ejaculation*	8%	1%
Impotence*	2%	1%
Decreased Libido	2%	1%
Anorgasmia	2%	0%

*Based on the number of male patients.

There are no adequate and well-controlled studies examining sexual dysfunction with fluvoxamine treatment.

Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	Other Events Observed During the Premarketing Evaluation of Fluvoxamine Maleate Tablets During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standard event categories. In the tabulations which follow, a standard COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 2, which tabulates incidence rates of common adverse experiences in placebo-controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring between 1/100 and 1/1000 patients; and rare adverse events are those occurring in less than 1/1000 patients. ***Body as a Whole:*** *Frequent:* accidental injury, malaise; *Infrequent:* allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; *Rare:* cyst, pelvic pain, sudden death. ***Cardiovascular System:*** *Frequent:* hypertension, hypotension, syncope, tachycardia; *Infrequent:* angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes: *Rare:* AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles. ***Digestive System:*** *Frequent:* elevated liver transaminases; *Infrequent:* colitis, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, gingivitis, glossitis, hemorrhoids, melena, rectal hemorrhage, stomatitis; *Rare:* biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice. ***Endocrine System:*** *Infrequent:* hypothyroidism; *Rare:* goiter. ***Hemic and Lymphatic Systems:*** *Infrequent:* anemia, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia: *Rare:* leukopenia, purpura ***Metabolic and Nutritional Systems:*** *Frequent:* edema, weight gain, weight loss; *Infrequent:* dehydration, hypercholesterolemia; *Rare:* diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased. ***Musculoskeletal System:*** *Infrequent:* arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis; *Rare:* arthrosis, myopathy, pathological fracture. ***Nervous System:*** *Frequent:* amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction; *Infrequent:* agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; *Rare:* akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome. ***Respiratory System:*** *Frequent:* cough increased, sinusitis; *Infrequent:* asthma, bronchitis, epistaxis, hoarseness, hyperventilation; *Rare:* apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia. ***Skin:*** *Infrequent:* acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin discoloration, urticaria. ***Special Senses:*** *Infrequent:* accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; *Rare:* corneal ulcer, retinal detachment ***Urogenital System:*** *Infrequent:* anuria, breast pain, cystitis, delayed menstruation[1], dysuria, female lactation[1], hematuria, menopause[1], menorrhagia[1], metrorrhagia[1], nocturia, polyuria, premenstrual

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	syndrome[1], urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginitis[1]; *Rare:* kidney calculus, hematospermia[2], oliguria. [1] Based on the number of females. [2] Based on the number of males. **Postmarketing Reports** Voluntary reports of adverse events in patients taking fluvoxamine maleate that have been received since market introduction and are of unknown causal relationship to fluvoxamine use include: ventricular tachycardia (including torsades de pointes), porphyria, toxic epidermal necrolysis, Stevens-Johnson syndrome, Henoch-Schoenlein purpura, bullous eruption, priapism, agranulocytosis, aplastic anemia, anaphylactic reaction, angioedema, amenorrhea, vasculitis, hyponatremia, acute renal failure, hepatitis, pancreatitis, ileus, serotonin syndrome, neuropathy, laryngismus, and severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
PAXIL® (PAROXETINE HYDROCHLORIDE)	**Associated With Discontinuation of Treatment:** Twenty percent (1,199/6,145) of patients treated with PAXIL in worldwide clinical trials in major depressive disorder and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients treated with PAXIL in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD, and PTSD, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for PAXIL compared to placebo) included the following:

	Major Depressive Disorder		OCD		Panic Disorder		Social Anxiety Disorder		Generalized Anxiety Disorder		PTSD	
	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo	PAXIL	Placebo
CNS												
Somnolence	2.3%	0.7%	—		1.9%	0.3%	3.4%	0.3%	2.0%	0.2%	2.8%	0.6%
Insomnia	—	—	1.7%	0%	1.3%	0.3%	3.1%	0%			—	—
Agitation	1.1%	0.5%	—								—	—
Tremor	1.1%	0.3%	—				1.7%	0%			1.0%	0.2%
Anxiety	—	—	—				1.1%	0%			—	—
Dizziness	—	—	1.5%	0%			1.9%	0%	1.0%	0.2%	—	—
Gastroin-testinal												
Constipation	—		1.1%	0%							—	—
Nausea	3.2%	1.1%	1.9%	0%	3.2%	1.2%	4.0%	0.3%	2.0%	0.2%	2.2%	0.6%
Diarrhea	1.0%	0.3%	—									
Dry mouth	1.0%	0.3%	—								—	—
Vomiting	1.0%	0.3%	—				1.0%	0%			—	—
Flatulence							1.0%	0.3%			—	—
Other												
Asthenia	1.6%	0.4%	1.9%	0.4%			2.5%	0.6%	1.8%	0.2%	1.6%	0.2%
Abnormal ejaculation[1]	1.6%	0%	2.1%	0%			4.9%	0.6%	2.5%	0.5%	—	—
Sweating	1.0%	0.3%	—				1.1%	0%	1.1%	0.2%	—	—
Impotence[1]	—		1.5%	0%							—	—
Libido Decreased							1.0%	0%			—	—

Where numbers are not provided the incidence of the adverse events in patients treated with PAXIL was not >1% or was not greater than or equal to 2 times the incidence of placebo.

1. Incidence corrected for gender.

Commonly Observed Adverse Events:

Major Depressive Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 2) were: Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

Obsessive Compulsive Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that of placebo, derived from Table 3) were: Nausea, dry mouth, decreased appetite, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

Panic Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 3) were: Asthenia, sweating, decreased appetite, libido decreased, tremor, abnormal ejaculation, female genital disorders, and impotence.

Social Anxiety Disorder: The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 3) were: Sweating, nausea, dry mouth, constipation, decreased appetite,

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders, and impotence. ***Generalized Anxiety Disorder:*** The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 4) were: Asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation. ***Posttraumatic Stress Disorder:*** The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 4) were: Asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence. **Incidence in Controlled Clinical Trials:** The prescriber should be aware that the figures in the tables following cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the populations studied. ***Major Depressive Disorder:*** Table 2 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder[1]

Body System	Preferred Term	PAXIL (n = 421)	Placebo (n = 421)
Body as a Whole	Headache	18%	17%
	Asthenia	15%	6%
Cardiovascular	Palpitation	3%	1%
	Vasodilation	3%	1%
Dermatologic	Sweating	11%	2%
	Rash	2%	1%
Gastrointestinal	Nausea	26%	9%
	Dry Mouth	18%	12%
	Constipation	14%	9%
	Diarrhea	12%	8%
	Decreased Appetite	6%	2%
	Flatulence	4%	2%
	Oropharynx Disorder[2]	2%	0%
	Dyspepsia	2%	1%
Musculoskeletal	Myopathy	2%	1%
	Myalgia	2%	1%
	Myasthenia	1%	0%
Nervous System	Somnolence	23%	9%
	Dizziness	13%	6%
	Insomnia	13%	6%
	Tremor	8%	2%
	Nervousness	5%	3%
	Anxiety	5%	3%
	Paresthesia	4%	2%
	Libido Decreased	3%	0%
	Drugged Feeling	2%	1%
	Confusion	1%	0%
Respiration	Yawn	4%	0%
Special Senses	Blurred Vision	4%	1%
	Taste Perversion	2%	0%
Urogenital System	Ejaculatory Disturbance[3,4]	13%	0%
	Other Male Genital Disorders[3,5]	10%	0%
	Urinary Frequency	3%	1%
	Urination Disorder[6]	3%	0%
	Female Genital Disorders[3,7]	2%	0%

1. Events reported by at least 1% of patients treated with PAXIL are included, except the following events which had an incidence on placebo ≥ PAXIL: Abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly "cold symptoms" or "URI"), trauma, and vomiting.
2. Includes mostly "lump in throat" and "tightness in throat."
3. Percentage corrected for gender.
4. Mostly "ejaculatory delay."
5. Includes "anorgasmia," "erectile difficulties," "delayed ejaculation/orgasm," and "sexual dysfunction," and "impotence."
6. Includes mostly "difficulty with micturition" and "urinary hesitancy."
7. Includes mostly "anorgasmia" and "difficulty reaching climax/orgasm."

Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder:
Table 3 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 60 mg/day or among patients with panic disorder on PAXIL who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10 mg to 60 mg/day or among patients with social anxiety disorder on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 50 mg/day.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder[1]

		Obsessive Compulsive Disorder		Panic Disorder		Social Anxiety Disorder	
Body System	Preferred Term	PAXIL (n = 542)	Placebo (n = 265)	PAXIL (n = 469)	Placebo (n = 324)	PAXIL (n = 425)	Placebo (n = 339)
Body as a Whole	Asthenia	22%	14%	14%	5%	22%	14%
	Abdominal Pain	—	—	4%	3%	—	—
	Chest Pain	3%	2%	—	—	—	—
	Back Pain	—	—	3%	2%	—	—
	Chills	2%	1%	2%	1%	—	—
	Trauma	—	—	—	—	3%	1%
Cardiovascular	Vasodilation	4%	1%	—	—	—	—
	Palpitation	2%	0%	—	—	—	—
Dermatologic	Sweating	9%	3%	14%	6%	9%	2%
	Rash	3%	2%	—	—	—	—
Gastrointestinal	Nausea	23%	10%	23%	17%	25%	7%
	Dry Mouth	18%	9%	18%	11%	9%	3%
	Constipation	16%	6%	8%	5%	5%	2%
	Diarrhea	10%	10%	12%	7%	9%	6%
	Decreased Appetite	9%	3%	7%	3%	8%	2%
	Dyspepsia	—	—	—	—	4%	2%
	Flatulence	—	—	—	—	4%	2%
	Increased Appetite	4%	3%	2%	1%	—	—
	Vomiting	—	—	—	—	2%	1%
Musculoskeletal	Myalgia	—	—	—	—	4%	3%
Nervous System	Insomnia	24%	13%	18%	10%	21%	16%
	Somnolence	24%	7%	19%	11%	22%	5%
	Dizziness	12%	6%	14%	10%	11%	7%
	Tremor	11%	1%	9%	1%	9%	1%
	Nervousness	9%	8%	—	—	8%	7%
	Libido Decreased	7%	4%	9%	1%	12%	1%
	Agitation	—	—	5%	4%	3%	1%
	Anxiety	—	—	5%	4%	5%	4%
	Abnormal Dreams	4%	1%	—	—	—	—
	Concentration Impaired	3%	2%	—	—	4%	1%
	Depersonalization	3%	0%	—	—	—	—
	Myoclonus	3%	0%	3%	2%	2%	1%
	Amnesia	2%	1%	—	—	—	—
Respiratory System	Rhinitis	—	—	3%	0%	—	—
	Pharyngitis	—	—	—	—	4%	2%
	Yawn	—	—	—	—	5%	1%
Special Senses	Abnormal Vision	4%	2%	—	—	4%	1%
	Taste Perversion	2%	0%	—	—	—	—
Urogenital System	Abnormal Ejaculation[2]	23%	1%	21%	1%	28%	1%
	Dysmenorrhea	—	—	—	—	5%	4%
	Female Genital Disorder[2]	3%	0%	9%	1%	9%	1%
	Impotence[2]	8%	1%	5%	0%	5%	1%
	Urinary Frequency	3%	1%	2%	0%	—	—
	Urination Impaired	3%	0%	—	—	—	—
	Urinary Tract Infection	2%	1%	2%	1%	—	—

1. Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients treated with PAXIL are included, except the following events which had an incidence on placebo ≥PAXIL: [OCD]: Abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis, and sinusitis. [panic disorder]: Abnormal dreams, abnormal vision, chest pain, cough

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired, and vasodilation. [social anxiety disorder]: Abdominal pain, depression, headache, infection, respiratory disorder, and sinusitis.

2. Percentage corrected for gender.

Generalized Anxiety Disorder and Posttraumatic Stress Disorder: Table 4 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on PAXIL who participated in placebo-controlled trials of 8-weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day or among PTSD patients on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg/day to 50 mg/day.

Table 4. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder[1]

		Generalized Anxiety Disorder		Posttraumatic Stress Disorder	
Body System	Preferred Term	PAXIL (n = 735)	Placebo (n = 529)	PAXIL (n = 676)	Placebo (n = 504)
Body as a Whole	Asthenia	14%	6%	12%	4%
	Headache	17%	14%	—	—
	Infection	6%	3%	5%	4%
	Abdominal Pain			4%	3%
	Trauma			6%	5%
Cardiovascular	Vasodilation	3%	1%	2%	1%
Dermatologic	Sweating	6%	2%	5%	1%
Gastrointestinal	Nausea	20%	5%	19%	8%
	Dry Mouth	11%	5%	10%	5%
	Constipation	10%	2%	5%	3%
	Diarrhea	9%	7%	11%	5%
	Decreased Appetite	5%	1%	6%	3%
	Vomiting	3%	2%	3%	2%
	Dyspepsia	—	—	5%	3%
Nervous System	Insomnia	11%	8%	12%	11%
	Somnolence	15%	5%	16%	5%
	Dizziness	6%	5%	6%	5%
	Tremor	5%	1%	4%	1%
	Nervousness	4%	3%	—	—
	Libido Decreased	9%	2%	5%	2%
	Abnormal Dreams			3%	2%
Respiratory System	Respiratory Disorder	7%	5%	—	—
	Sinusitis	4%	3%	—	—
	Yawn	4%	—	2%	<1%
Special Senses	Abnormal Vision	2%	1%	3%	1%
Urogenital System	Abnormal Ejaculation[2]	25%	2%	13%	2%
	Female Genital Disorder[2]	4%	1%	5%	1%
	Impotence[2]	4%	3%	9%	1%

1. Events reported by at least 2% of GAD and PTSD in patients treated with PAXIL are included, except the following events which had an incidence on placebo ≥PAXIL [GAD]: Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis. [PTSD]: Back pain, headache, anxiety, depression, nervousness, respiratory disorder, pharyngitis, and sinusitis.
2. Percentage corrected for gender.

Dose Dependency of Adverse Events: A comparison of adverse event rates in a fixed-dose study comparing 10, 20, 30, and 40 mg/day of PAXIL with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with use of PAXIL, as shown in the following table:

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 5 . Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder*

Body System/Preferred Term	Placebo n = 51	PAXIL 10 mg n = 102	PAXIL 20 mg n = 104	PAXIL 30 mg n = 101	PAXIL 40 mg n = 102
Body as a Whole					
Asthenia	0.0%	2.9%	10.6%	13.9%	12.7%
Dermatology					
Sweating	2.0%	1.0%	6.7%	8.9%	11.8%
Gastrointestinal					
Constipation	5.9%	4.9%	7.7%	9.9%	12.7%
Decreased Appetite	2.0%	2.0%	5.8%	4.0%	4.9%
Diarrhea	7.8%	9.8%	19.2%	7.9%	14.7%
Dry Mouth	2.0%	10.8%	18.3%	15.8%	20.6%
Nausea	13.7%	14.7%	26.9%	34.7%	36.3%
Nervous System					
Anxiety	0.0%	2.0%	5.8%	5.9%	5.9%
Dizziness	3.9%	6.9%	6.7%	8.9%	12.7%
Nervousness	0.0%	5.9%	5.8%	4.0%	2.9%
Paresthesia	0.0%	2.9%	1.0%	5.0%	5.9%
Somnolence	7.8%	12.7%	18.3%	20.8%	21.6%
Tremor	0.0%	0.0%	7.7%	7.9%	14.7%
Special Senses					
Blurred Vision	2.0%	2.9%	2.9%	2.0%	7.8%
Urogenital System					
Abnormal Ejaculation	0.0%	5.8%	6.5%	10.6%	13.0%
Impotence	0.0%	1.9%	4.3%	6.4%	1.9%
Male Genital Disorders	0.0%	3.8%	8.7%	6.4%	3.7%

* Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups and ≥ twice the placebo incidence for at least 1 paroxetine group.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of OCD, there was no clear relationship between adverse events and the dose of PAXIL to which patients were assigned. No new adverse events were observed in the group treated with 60 mg of PAXIL compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 10, 20, and 40 mg of PAXIL in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of PAXIL to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in patients receiving 60 mg of PAXIL compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of social anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of PAXIL to which patients were assigned.

In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of generalized anxiety disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of PAXIL to which patients were assigned, except for the following adverse events: Asthenia, constipation, and abnormal ejaculation.

In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of posttraumatic stress disorder, for most of the adverse events, there was no clear relationship between adverse events and the dose of PAXIL to which patients were assigned, except for impotence and abnormal ejaculation.

Adaptation to Certain Adverse Events: Over a 4- to 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less to other effects (e.g., dry mouth, somnolence, and asthenia).

Male and Female Sexual Dysfunction With SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire,

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the reported incidence of sexual side effects in males and females with major depressive disorder, OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 6.

Table 6. Incidence of Sexual Adverse Events in Controlled Clinical Trials

	PAXIL	Placebo
n (males)	**1446**	**1042**
Decreased Libido	6-15%	0-5%
Ejaculatory Disturbance	13-28%	0-2%
Impotence	2-9%	0-3%
n (females)	**1822**	**1340**
Decreased Libido	0-9%	0-2%
Orgasmic Disturbance	2-9%	0-1%

There are no adequate and well-controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with PAXIL for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with PAXIL in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with PAXIL and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In placebo-controlled clinical trials, patients treated with PAXIL exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the PAXIL-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients receiving placebo.

Other Events Observed During the Premarketing Evaluation of PAXIL: During its premarketing assessment in major depressive disorder, multiple doses of PAXIL were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to PAXIL varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose, and titration studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676 patients, respectively, received multiple doses of PAXIL. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9,089 patients exposed to multiple doses of PAXIL who experienced an event of the type cited on at least 1 occasion while receiving PAXIL. All reported events are included except those already listed in Tables 2 to 4, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events of major clinical importance are also described in the PRECAUTIONS section. ***Body as a Whole:*** *Infrequent:* Allergic reaction, chills, face edema, malaise, neck pain; *rare:* Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer. ***Cardiovascular System:*** *Frequent:* Hypertension, tachycardia; *infrequent:* Bradycardia, hematoma, hypotension, migraine, postural hypotension, syncope; *rare:* Angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles. ***Digestive System:*** *Infrequent:* Bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* Aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries. ***Endocrine System:*** *Rare:* Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis. ***Hemic and Lymphatic Systems:*** *Infrequent:* Anemia, leukopenia, lymphadenopathy, purpura; *rare:* Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia. ***Metabolic and Nutritional:*** *Frequent:* Weight gain; *infrequent:* Edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; *rare:* Alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased. ***Musculoskeletal System:*** *Frequent:* Arthralgia; *infrequent:* Arthritis, arthrosis; *rare:* Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany. ***Nervous System:*** *Frequent:* Emotional lability, vertigo; *infrequent:* Abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; *rare:* Abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome. ***Respiratory System:*** *Infrequent:* Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration. ***Skin and Appendages:*** *Frequent:* Pruritus; *infrequent:* Acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis; herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. ***Special Senses:*** *Frequent*: Tinnitus; *infrequent:* Abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect. ***Urogenital System:*** *Infrequent:* Amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis,

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis. **Postmarketing Reports:** Voluntary reports of adverse events in patients taking PAXIL that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome–like events, serotonin syndrome; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of PAXIL and phenytoin coadministration. There has been a case report of severe hypotension when PAXIL was added to chronic metoprolol treatment.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
PAXIL® CR (paroxetine hydrochloride) Extended-Release Capsules	The information included under the "Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL CR" subsection of ADVERSE REACTIONS is based on data from 11 placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, 3 studies were done in patients with panic disorder, 1 study was conducted in patients with social anxiety disorder, and 4 studies were done in female patients with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60 to 88 years), is presented separately as is the information from the panic disorder studies and the information from the PMDD studies. Information on additional adverse events associated with PAXIL CR and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see Other Events). **Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With PAXIL CR:** **Adverse Events Associated With Discontinuation of Treatment: *Major Depressive Disorder:*** Ten percent (21/212) of patients treated with PAXIL CR discontinued treatment due to an adverse event in a pool of 2 studies of patients with major depressive disorder. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for PAXIL CR compared to placebo) included the following: **PAXIL CR (n = 212)** / **Placebo (n = 211)** Nausea 3.7% / 0.5% Asthenia 1.9% / 0.5% Dizziness 1.4% / 0.0% Somnolence 1.4% / 0.0% In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of patients treated with PAXIL CR discontinued due to an adverse event. Events meeting the above criteria included the following: **PAXIL CR (n = 104)** / **Placebo (n = 109)** Nausea 2.9% / 0.0% Headache 1.9% / 0.9% Depression 1.9% / 0.0% LFT's abnormal 1.9% / 0.0% ***Panic Disorder:*** Eleven percent (50/444) of patients treated with PAXIL CR in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included the following: **PAXIL CR (n = 444)** / **Placebo (n = 445)** Nausea 2.9% / 0.4% Insomnia 1.8% / 0.0% Headache 1.4% / 0.2% Asthenia 1.1% / 0.0% ***Social Anxiety Disorder:*** Three percent (5/186) of patients treated with PAXIL CR in the social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the above criteria included the following: **PAXIL CR (n = 186)** / **Placebo (n = 184)** Nausea 2.2% / 0.5% Headache 1.6% / 0.5% Diarrhea 1.1% / 0.5% ***Premenstrual Dysphoric Disorder:*** Spontaneously reported adverse events were monitored in studies of both continuous and intermittent dosing of PAXIL CR in the treatment of PMDD.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Generally, there were few differences in the adverse event profiles of the 2 dosing regimens. Thirteen percent (88/681) of patients treated with PAXIL CR in PMDD studies of continuous dosing discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation in either group treated with PAXIL CR with an incidence rate that is at least twice that of placebo in PMDD trials that employed a continuous dosing regimen are shown in the following table. This table also shows those events that were dose dependent (indicated with an asterisk) as defined as events having an incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the placebo group).

	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
TOTAL	15%	9.9%	6.3%
Nausea*	6.0%	2.4%	0.9%
Asthenia	4.9%	3.0%	1.4%
Somnolence*	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	0.0%
Concentration Impaired*	2.0%	0.6%	0.3%
Dry mouth*	2.0%	0.6%	0.3%
Dizziness*	1.7%	0.6%	0.6%
Decreased Appetite*	1.4%	0.6%	0.0%
Sweating*	1.4%	0.0%	0.3%
Tremor*	1.4%	0.3%	0.0%
Yawn*	1.1%	0.0%	0.0%
Diarrhea	0.9%	1.2%	0.0%

* Events considered to be dose dependent are defined as events having an incidence rate with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR (as well as the placebo group).

Commonly Observed Adverse Events:

Major Depressive Disorder*:* The most commonly observed adverse events associated with the use of PAXIL CR in a pool of 2 trials (incidence of 5.0% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 2) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning. Using the same criteria, the adverse events associated with the use of PAXIL CR in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Panic Disorder*:* In the pool of panic disorder studies, the adverse events meeting these criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating, and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder: In the social anxiety disorder study, the adverse events meeting these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia, and libido decreased.

Premenstrual Dysphoric Disorder*:* The most commonly observed adverse events associated with the use of PAXIL CR either during continuous dosing or luteal phase dosing (incidence of 5% or greater and incidence for PAXIL CR at least twice that for placebo, derived from Table 6) were: Nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea, and constipation. In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day of PAXIL CR limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the 3 off-drug phases were combined, the following adverse events were reported at an incidence of 2% or greater for PAXIL CR and were at least twice the rate of that reported for placebo: Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%), sinusitis (2.4% versus 0%), and asthenia (2.0% versus 0.8%).

Incidence in Controlled Clinical Trials: Table 2 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with PAXIL CR, aged 18 to 65, who participated in 2 short-term (12-week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 3 enumerates adverse events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated with PAXIL CR who participated in a short-term (12-week) placebo-controlled trial in major depressive disorder in

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 4 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72 years) treated with PAXIL CR who participated in short-term (10-week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 5 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with PAXIL CR who participated in a short-term (12-week), double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day. Table 6 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with PAXIL CR who participated in three 12-week placebo-controlled trials in PMDD in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

TABLE 2. TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN ≥1% OF PATIENTS TREATED WITH PAXIL CR IN A POOL OF 2 STUDIES IN MAJOR DEPRESSIVE DISORDER[1,2]

Body System/ Adverse Event	% Reporting Event	
	PAXIL CR (n=212)	Placebo (n=211)
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection[1]	8%	5%
Abdominal Pain	7%	4%
Back pain	5%	3%
Trauma[4]	5%	1%
Pain[5]	3%	1%
Allergic Reaction[6]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilation[7]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

BODY SYSTEM/ ADVERSE EVENT	% REPORTING EVENT	
	PAXIL CR (N=212)	PLACEBO (N=211)
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal ejaculation[9,10]	26%	1%
Female Genital Disorder[9,11]	10%	<1%
Impotence[9]	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder[9]	2%	<1%
Vaginitis[9]	2%	0%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
2. <1% means greater than zero and less than 1%.
3. Mostly flu.
4. A wide variety of injuries with no obvious pattern.
5. Pain in a variety of locations with no obvious pattern.
6. Most frequently seasonal allergic symptoms.
7. Usually flushing.
8. Mostly blurred vision.
9. Based on the number of males or females.
10. Mostly anorgasmia or delayed ejaculation.
11. Mostly anorgasmia or delayed orgasm.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

TABLE 3. TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN ≥5% OF PATIENTS TREATED WITH PAXIL CR IN A STUDY OF ELDERLY PATIENTS WITH MAJOR DEPRESSIVE DISORDER[1,2]

Body System/ Adverse Event	% Reporting Event	
	PAXIL CR (n=104)	Placebo (n=109)
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal ejaculation[3,4]	17%	3%
Impotence[3]	9%	3%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to the placebo reporting incidence are not included. These events are nausea and respiratory disorder.
2. <1% means greater than zero and less than 1%.
3. Based on the number of males.
4. Mostly anorgasmia or delayed ejaculation.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

TABLE 4. TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN ≥1% OF PATIENTS TREATED WITH PAXIL CR IN A POOL OF 3 PANIC DISORDER STUDIES[1,2]

Body System/ Adverse Event	% Reporting Event	
	PAXIL CR (n=444)	Placebo (n=445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma[3]	5%	4%
Cardiovascular System		
Vasodilation[4]	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%
Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia[5]	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision[6]	3%	<1%
Urogenital System		
Abnormal ejaculation[7,8]	27%	3%
Impotence[7]	10%	1%
Female Genital Disorders[9,10]	7%	1%

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Body System/ Adverse Event	**% Reporting Event**	
	PAXIL CR (n=212)	**Placebo (n=211)**
Vaginitis[9]	1%	<1%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to placebo incidence are not included. These events are: Abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection, and vomiting.
2. <1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Mostly flushing
5. Mostly muscle tightness or stiffness.
6. Mostly blurred vision.
7. Based on the number or male patients.
8. Mostly anorgasmia or delayed ejaculation.
9. Based on the number of female patients.

TABLE 5. TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN ≥1% OF PATIENTS TREATED WITH PAXIL CR IN A SOCIAL ANXIETY DISORDER STUDY[1,2]

Body System/ Adverse Event	% Reporting Event	
	PAXIL CR (n=186)	Placebo (n=184)
Body as a Whole		
Headache	28%	17%
Asthenia	18%	7%
Abdominal Pain	5%	4%
Back pain	4%	1%
Trauma[3]	3%	<1%
Allergic Reaction[4]	2%	<1%
Chest Pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry Mouth	3%	2%
Dyspepsia	2%	<1%
Decreased Appetite	1%	<1%
Tooth Disorder	1%	0%
Metabolic/Nutritional Disorders		

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Weight Gain	3%	1%
Body System/ Adverse Event	**% Reporting Event**	
	PAXIL CR (n=212)	**Placebo (n=211)**
Weight Loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido Decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration Impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%
Special Senses		
Abnormal Vision[5]	2%	0%
Abnormality of Accommodation	2%	0%
Urogenital System		
Abnormal ejaculation[6,7]	15%	1%
Impotence[6]	9%	0%
Female Genital Disorders[8,9]	3%	0%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to placebo incidence are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis, hypertonia, infection, pain, paresthesia, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.
2. <1% means greater than zero and less than 1%.
3. Various physical injuries.
4. Most frequently seasonal allergic symptoms.
5. Mostly blurred vision.
6. Based on the number of male patients.
7. Mostly anorgasmia or delayed ejaculation.
8. Based on the number of female patients.
9. Mostly anorgasmia or difficulty achieving orgasm.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

TABLE 6. TREATMENT-EMERGENT ADVERSE EVENTS OCCURRING IN ≥1% OF PATIENTS TREATED WITH PAXIL CR IN A POOL OF 3 PREMENSTRUAL DYSPHORIC DISORDER STUDIES WITH CONTINUOUS DOSING OR IN 1 PREMENSTRUAL DYSPHORIC STUDY WITH LUTEAL PHASE DOSING[1,2,3]

Body System / Adverse Event	% Reporting Event			
	Continuous Dosing		Luteal Phase Dosing	
	PAXIL CR (n=681)	Placebo (n=349)	PAXIL CR (n=246)	Placebo (n=120)
Body as a Whole				
Asthenia	17%	6%	15%	4%
Headache	15%	12%	__	__
Infection	6%	4%	__	__
Abdominal Pain	__	__	3%	0%
Cardiovascular System				
Migraine	1%	<1%	__	__
Digestive System				
Nausea	17%	7%	18%	2%
Diarrhea	6%	2%	6%	0%
Constipation	5%	1%	2%	<1%
Dry Mouth	4%	2%	2%	<1%
Increased Appetite	3%	<1%	__	__
Decreased Appetite	2%	<1%	2%	0%
Dyspepsia	2%	1%	2%	2%
Gingivitis	__	__	1%	0%
Metabolic & Nutritional Disorders				
Generalized Edema	__	__	1%	<1%
Weight Gain	__	__	1%	<1%
Musculoskeletal System				
Arthralgia	2%	1%	__	__
Nervous System				
Libido Decreased	12%	5%	9%	6%
Somnolence	9%	2%	3%	<1%
Insomnia	8%	2%	7%	3%
Dizziness	7%	3%	6%	3%
Tremor	4%	<1%	5%	0%
Concentration Impaired	3%	<1%	1%	0%
Nervousness	2%	<1%	3%	2%
Anxiety	2%	1%	__	__
Lack of Emotion	2%	<1%	__	__
Depression	__	___	2%	<1%
Vertigo	__	__	2%	<1%
Abnormal Dreams	1%	<1%	__	__
Amnesia	__	__	1%	0%

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Body System / Adverse Event	% Reporting Event			
	Continuous Dosing		Luteal Phase Dosing	
	PAXIL CR (n=681)	Placebo (n=349)	PAXIL CR (n=246)	Placebo (n=120)
Respiratory System				
Sinusitis	—	—	4%	2%
Yawn	2%	<1%	—	—
Bronchitis	—	—	2%	0%
Cough Increased	1%	<1%	—	—
Skin and Appendages				
Sweating	7%	<1%	6%	<1%
Special Senses				
Abnormal Vision	—	—	1%	0%
Urogenital System				
Female Genital Disorders	8%	1%	2%	0%
Menorrhagia	1%	<1%	—	—
Vaginal Moniliasis	1%	<1%	—	—
Menstrual Disorder	—	—	1%	0%

1. Adverse events for which the PAXIL CR reporting incidence was less than or equal to placebo incidence are not included. These events for continuous dosing are: Abdominal pain, back pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis, pruritis, dysmenorrhea, menstrual disorder, urinary tract infection, and vomiting. The events for luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma, myalgia, anxiety, pharyngitis, respiratory disorder, cystitis, and dysmenorrhea.
2. <1% means greater than zero and less than 1%.
3. The luteal phase and continuous dosing PMDD trials were not designed for making direct comparisons between the 2 dosing regimens. Therefore, a comparison between the 2 dosing regimens for PMDD trials of incidence rates shown in Table 6 should be avoided.
4. Mostly anorgasmia or difficulty achieving orgasm.

Dose Dependency of Adverse Events: The following table shows results in PMDD trials of common adverse events, defined as events with an incidence of ≥1% with 25 mg of PAXIL CR that was at least twice that with 12.5 mg of PAXIL CR and with placebo.

Incidence of Common Adverse Events in Placebo, 12.5 mg and 25 mg of PAXIL CR in a Pool of 3 Fixed-Dose PMDD Trials

	PAXIL CR 25 mg (n = 348)	PAXIL CR 12.5 mg (n = 333)	Placebo (n = 349)
Common Adverse Event			
Sweating	8.9%	4.2%	0.9%
Tremor	6.0%	1.5%	0.3%
Concentration Impaired	4.3%	1.5%	0.6%
Yawn	3.2%	0.9%	0.3%
Paresthesia	1.4%	0.3%	0.3%
Hyperkinesia	1.1%	0.3%	0.0%
Vaginitis	1.1%	0.3%	0.3%

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

A comparison of adverse event rates in a fixed-dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

Male and Female Sexual Dysfunction With SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain; however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

The percentage of patients reporting symptoms of sexual dysfunction in the pool of 2 placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of 3 placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients with social anxiety disorder, and in the intermittent dosing and the pool of 3 placebo-controlled continuous dosing trials in female patients with PMDD are as follows:

	Major Depressive Disorder		Panic Disorder		Social Anxiety Disorder		PMDD Continuous Dosing		PMDD Luteal Phase Dosing	
	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo	PAXIL CR	Placebo
n (males)	**78**	**78**	**162**	**194**	**88**	**97**	**n/a**	**n/a**	**n/a**	**n/a**
Decreased Libido	10%	5%	9%	6%	13%	1%	n/a	n/a	n/a	n/a
Ejaculatory Disturbance	26%	1%	27%	3%	15%	1%	n/a	n/a	n/a	n/a
Impotence	5%	3%	10%	1%	9%	0%	n/a	n/a	n/a	n/a
n (females)	**134**	**133**	**282**	**251**	**98**	**87**	**681**	**349**	**246**	**120**
Decreased Libido	4%	2%	8%	2%	4%	1%	12%	5%	9%	6%
Orgasmic Disturbance	10%	<1%	7%	1%	3%	0%	8%	1%	2%	0%

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with PAXIL CR or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) were observed in patients treated with PAXIL CR, or immediate-release paroxetine hydrochloride, in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In a pool of 2 placebo-controlled clinical trials, patients treated with PAXIL CR or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the controlled-release paroxetine-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with PAXIL

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	CR and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern. Two of the patients treated with PAXIL CR dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of 3 studies of patients with panic disorder, 4 of 444 patients treated with PAXIL CR and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all 4 patients decreased substantially after discontinuation of PAXIL CR. The clinical significance of these findings is unknown. In placebo-controlled clinical trials with the immediate-release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. ***Hallucinations*:** In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients receiving placebo. **Other Events Observed During the Clinical Development of Paroxetine:** The following adverse events were reported during the clinical development of PAXIL CR and/or the clinical development of the immediate-release formulation of paroxetine. Adverse events for which frequencies are provided below occurred in clinical trials with the controlled-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder, social anxiety disorder, and PMDD, multiple doses of PAXIL CR were administered to 1,627 patients in phase 3 double-blind, controlled, outpatient studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that follow, reported adverse events were classified using a COSTART-based dictionary. The frequencies presented, therefore, represent the proportion of the 1,627 patients exposed to PAXIL CR who experienced an event of the type cited on at least 1 occasion while receiving PAXIL CR. All reported events are included except those already listed in Tables 2 through 6 and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase 2 and 3 studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose and titration studies. Only those events not previously listed for controlled-release paroxetine are included. The extent to which these events may be associated with PAXIL CR is unknown. Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in the PRECAUTIONS section. ***Body as a Whole:*** Infrequent were chills, face edema, fever, flu syndrome, malaise; rare were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis. ***Cardiovascular System:*** Infrequent were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles. ***Digestive System:*** Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena,

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema. ***Endocrine System:*** Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis. ***Hemic and Lymphatic System:*** Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia. ***Metabolic and Nutritional Disorders:*** Infrequent were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased. ***Musculoskeletal System:*** Infrequent were arthritis, bursitis, tendonitis; rare were myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany. ***Nervous System:*** Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus. ***Respiratory System:*** Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased. ***Skin and Appendages:*** Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. ***Special Senses:*** Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss. ***Urogenital System:*** Frequent were dysmenorrheal*; infrequent were albuminuria, amenorrhea* breast pain*, cystitis, dysuria, prostatitis* urinary retention; rare were breast* enlargement* breast neoplasm* female lactation, hematuria*, kidney calculus, metrorrhagia , nephritis, nocturia, pregnancy and puerperal disorders , salpingitis, urinary incontinence, uterine fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage. *Based on the number of men and women as appropriate. **Postmarketing Reports***:* Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome–like events, serotonin syndrome; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.
Prozac® (fluoxetine hydrochloride)	Multiple doses of Prozac had been administered to 10,782 patients with various diagnoses in US clinical trials as of May 8, 1995. In addition, there have been 425 patients administered Prozac in panic clinical trials. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories. In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied. ***Incidence in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials):***Table 2 enumerates the most common treatment-emergent adverse events associated with the use of Prozac (incidence of at least 5% for Prozac and at least twice that for placebo within at least 1 of the indications) for the treatment of major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder in US plus non-US controlled trials. Table 3 enumerates treatment-emergent adverse events that occurred in 2% or more patients treated with Prozac and with incidence greater than placebo who participated in US major depressive disorder, OCD, and bulimia controlled clinical trials and US plus non-US panic disorder controlled clinical trials. Table 3 provides combined data for the pool of studies that are provided separately by indication in Table 2. **Table 2: Most Common Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]** Percentage of Patients Reporting Event Major Depressive Disorder: Prozac (N=1728), Placebo (N=975) OCD: Prozac (N=266), Placebo (N=89) Bulimia: Prozac (N=450), Placebo (N=267) Panic Disorder: Prozac (N=425), Placebo (N=342) **Body System/ Adverse Event** **Body as a Whole** Asthenia: 9, 5, 15, 11, 21, 9, 7, 7 Flu syndrome: 3, 4, 10, 7, 8, 3, 5, 5 **Cardiovascular System** Vasodilatation: 3, 2, 5, --, 2, 1, 1, -- **Digestive System** Nausea: 21, 9, 26, 13, 29, 11, 12, 7 Diarrhea: 12, 8, 18, 13, 8, 6, 9, 4 Anorexia: 11, 2, 17, 10, 8, 4, 4, 1 Dry mouth: 10, 7, 12, 3, 9, 6, 4, 4 Dyspepsia: 7, 5, 10, 4, 10, 6, 6, 2 **Nervous System** Insomnia: 16, 9, 28, 22, 33, 13, 10, 7 Anxiety: 12, 7, 14, 7, 15, 9, 6, 2 Nervousness: 14, 9, 14, 15, 11, 5, 8, 6 Somnolence: 13, 6, 17, 7, 13, 5, 5, 2 Tremor: 10, 3, 9, 1, 13, 1, 3, 1 Libido decreased: 3, --, 11, 2, 5, 1, 1, 2 Abnormal dreams: 1, 1, 5, 2, 5, 3, 1, 1 **Respiratory System** Pharyngitis: 3, 3, 11, 9, 10, 5, 3, 3 Sinusitis: 1, 4, 5, 2, 6, 4, 2, 3 Yawn: --, --, 7, --, 11, --, 1, -- **Skin and Appendages** Sweating: 8, 3, 7, --, 8, 3, 2, 2 Rash: 4, 3, 6, 3, 4, 4, 2, 2 **Urogenital System** Impotence[2]: 2, --, --, --, 7, --, 1, -- Abnormal ejaculation[2]: --, --, 7, --, 7, --, 2, 1 [1] Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials. [2] Denominator used was for males only (N=690 Prozac major depressive disorder; N=410 placebo major depressive disorder; N=116 Prozac OCD; N=43 placebo OCD; N=14 Prozac bulimia; N=1 placebo bulimia; N=162 Prozac panic; N=121 placebo panic). -- Incidence less than 1%.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 3: Treatment-Emergent Adverse Events: Incidence in Major Depressive Disord OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event	
	Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined	
Body System/ Adverse Event[2]	Prozac (N=2869)	Placebo (N=1673)
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6
Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	1
Thinking abnormal	2	1
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	7	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	2	1

[1] Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.

[2] Included are events reported by at least 2% of patients taking Prozac, except the following events, which had an incidence on placebo ≥ Prozac (major depressive disorder, OCD, bulimia, and panic disorder combined): abdominal pain, abnormal dreams, accidental injury, back pain, cough increased, major depressive disorder (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitis.

-- Incidence less than 1%.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Associated with discontinuation in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials): Table 4 lists the adverse events associated with discontinuation of Prozac treatment (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Table 4: Most Common Adverse Events Associated with Discontinuation in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined (N=1533)	Major Depressive Disorder (N=392)	OCD (N=266)	Bulimia (N=450)	Panic Disorder (N=425)
Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
--	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)
--	--	Rash (1%)	--	--

[1] Includes US major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Other adverse events in pediatric patients (children and adolescents): Treatment-emergent adverse events were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 2 and 3. However, the following adverse events (excluding those which appear in the body or footnotes of Tables 2 and 3 and those for which the COSTART terms were uninformative or misleading) were reported at an incidence of at least 2% for fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia.

The most common adverse event (incidence at least 1% for fluoxetine and greater than placebo) associated with discontinuation in 3 pediatric placebo-controlled trials (N=418 randomized; 228 fluoxetine-treated; 190 placebo-treated) was mania/hypomania (1.8% for fluoxetine-treated, 0% for placebo-treated). In these clinical trials, only a primary event associated with discontinuation was collected.

Events observed in Prozac Weekly clinical trials: Treatment-emergent adverse events in clinical trials with Prozac Weekly were similar to the adverse events reported by patients in clinical trials with Prozac daily. In a placebo-controlled clinical trial, more patients taking Prozac Weekly reported diarrhea than patients taking placebo (10% versus 3%, respectively) or taking Prozac 20 mg daily (10% versus 5%, respectively).

Male and female sexual dysfunction with SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in US major depressive disorder, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	Other Events Observed in Clinical Trials Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials as of May 8, 1995 (10,782 patients) except (1) those listed in the body or footnotes of Tables 2 or 3 above or elsewhere in labeling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to Prozac use was considered remote; and (4) events occurring in only 1 patient treated with Prozac and which did not have a substantial probability of being acutely life-threatening. Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients. **Body as a Whole** — *Frequent:* chest pain, chills; *Infrequent:* chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare:* acute abdominal syndrome, hypothermia, intentional injury, neuroleptic malignant syndrome[1], photosensitivity reaction. **Cardiovascular System** — *Frequent:* hemorrhage, hypertension, palpitation; *Infrequent:* angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache; *Rare:* atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation. **Digestive System** — *Frequent:* increased appetite, nausea and vomiting; *Infrequent:* aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare:* biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema. **Endocrine System** — *Infrequent:* hypothyroidism; *Rare:* diabetic acidosis, diabetes mellitus. **Hemic and Lymphatic System** — *Infrequent:* anemia, ecchymosis; *Rare:* blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia. **Metabolic and Nutritional** — *Frequent:* weight gain; *Infrequent:* dehydration, generalized edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare:* alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased. **Musculoskeletal System** — *Infrequent:* arthritis, bone pain, bursitis, leg cramps, tenosynovitis; *Rare:* arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis. **Nervous System** — *Frequent:* agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder[2], psychosis, vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor. **Respiratory System** — *Infrequent:* asthma, epistaxis, hiccup, hyperventilation; *Rare:* apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor. **Skin and Appendages** — *Infrequent:* acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare:* furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea. **Special Senses** — *Frequent:* ear pain, taste perversion, tinnitus; *Infrequent:* conjunctivitis, dry eyes, mydriasis, photophobia; *Rare:* blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect. **Urogenital System** — *Frequent:* urinary frequency; *Infrequent:* abortion,[3] albuminuria,

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	amenorrhea[3], anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation,[3] fibrocystic breast,[3] hematuria, leucorrhea,[3] menorrhagia,[3] metrorrhagia,[3] nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage;[3] *Rare:* breast engorgement, glycosuria, hypomenorrhea,[3] kidney pain, oliguria, priapism,[3] uterine hemorrhage,[3] uterine fibroids enlarged.[3] [1] Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome. [2] Personality disorder is the COSTART term for designating nonaggressive objectionable behavior. [3] Adjusted for gender. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema multiforme, erythema nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
ZOLOFT® (sertraline hydrochloride)	During its premarketing assessment, multiple doses of ZOLOFT were administered to over 4000 adult subjects as of February 18, 2000. The conditions and duration of exposure to ZOLOFT varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for multiple indications, including major depressive disorder, OCD, panic disorder, PTSD, PMDD, and social anxiety disorder. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving ZOLOFT. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied. **Incidence in Placebo-Controlled Trials–**Table 1 enumerates the most common treatment emergent adverse events associated with the use of ZOLOFT (incidence of at least 5% for ZOLOFT and at least twice that for placebo within at least one of the indications) for the treatment of adult patients with major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD, and social anxiety disorder in placebo-controlled clinical trials. Most patients in major depressive disorder/other*, OCD, panic disorder, PTSD, and social anxiety disorder studies received doses of 50 to 200 mg/day. Patients in the PMDD study with daily dosing throughout the menstrual cycle received doses of 50 to 150 mg/day, and in the PMDD study with dosing during the luteal phase of the menstrual cycle received doses of 50 to 100 mg/day. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more of adult patients treated with ZOLOFT and with incidence greater than placebo who participated in controlled clinical trials comparing ZOLOFT with placebo in the treatment of major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD, and social anxiety disorder. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

TABLE 1
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event							
	Major Depressive Disorder/Other*		OCD		Panic Disorder		PTSD	
Body System/Adverse Event	ZOLOFT (N=861)	Placebo (N=853)	ZOLOFT (N=533)	Placebo (N=373)	ZOLOFT (N=430)	Placebo (N=275)	ZOLOFT (N=374)	Placebo (N=376)
Autonomic Nervous System Disorders								
Ejaculation Failure(1)	7	<1	17	2	19	1	11	1
Mouth Dry	16	9	14	9	15	10	11	6
Sweating Increased	8	3	6	1	5	1	4	2
Centr. & Periph. Nerv. System Disorders								
Somnolence	13	6	15	8	15	9	13	9
Tremor	11	3	8	1	5	1	5	1
Dizziness	12	7	17	9	10	10	8	5
General								
Fatigue	11	8	14	10	11	6	10	5
Pain	1	2	3	1	3	3	4	6
Malaise	<1	1	1	1	7	14	10	10
Gastrointestinal Disorders								
Abdominal Pain	2	2	5	5	6	7	6	5
Anorexia	3	2	11	2	7	2	8	2
Constipation	8	6	6	4	7	3	3	3
Diarrhea/Loose Stools	18	9	24	10	20	9	24	15
Dyspepsia	6	3	10	4	10	8	6	6
Nausea	26	12	30	11	29	18	21	11
Psychiatric Disorders								
Agitation	6	4	6	3	6	2	5	5
Insomnia	16	9	28	12	25	18	20	11
Libido Decreased	1	<1	11	2	7	1	7	2
	PMDD Daily Dosing		PMDD Luteal Phase Dosing(2)		Social Anxiety Disorder			
Body System/Adverse Event	ZOLOFT (N=121)	Placebo (N=122)	ZOLOFT (N=136)	Placebo (N=127)	ZOLOFT (N=344)	Placebo (N=268)		
Autonomic Nervous System Disorders								
Ejaculation Failure(1)	N/A	N/A	N/A	N/A	14	-		
Mouth Dry	6	3	10	3	12	4		
Sweating Increased	6	<1	3	0	11	2		
Centr. & Periph. Nerv. System Disorders								
Somnolence	7	<1	2	0	9	6		
Tremor	2	0	<1	<1	9	3		
Dizziness	6	3	7	5	14	6		
General								
Fatigue	16	7	10	<1	12	6		
Pain	6	<1	3	2	1	3		
Malaise	9	5	7	5	8	3		
Gastrointestinal Disorders								
Abdominal Pain	7	<1	3	3	5	5		
Anorexia	3	2	5	0	6	3		
Constipation	2	3	1	2	5	3		
Diarrhea/Loose Stools	13	3	13	7	21	8		
Dyspepsia	7	2	7	3	13	5		
Nausea	23	9	13	3	22	8		
Psychiatric Disorders								
Agitation	2	<1	1	0	4	2		
Insomnia	17	11	12	10	25	10		
Libido Decreased	11	2	4	2	9	3		

(1)Primarily ejaculatory delay. Denominator used was for male patients only (N=271 ZOLOFT major depressive disorder/other*; N=271 placebo major depressive disorder/other*; N=296 ZOLOFT OCD; N=219 placebo OCD; N=216 ZOLOFT panic disorder; N=134 placebo panic disorder; N=130 ZOLOFT PTSD; N=149 placebo PTSD; No male patients in PMDD studies; N=205 ZOLOFT social anxiety disorder; N=153 placebo social anxiety disorder).
*Major depressive disorder and other premarketing controlled trials.
(2)The luteal phase and daily dosing PMDD trials were not designed for making direct comparisons between the two dosing regimens. Therefore, a comparison between the two dosing

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

regimens of the PMDD trials of incidence rates shown in Table 1 should be avoided.

TABLE 2
TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS
Percentage of Patients Reporting Event
Major Depressive Disorder/Other*, OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined

Body System/Adverse Event**	ZOLOFT (N=2799)	Placebo (N=2394)
Autonomic Nervous System Disorders		
Ejaculation Failure[1]	14	1
Mouth Dry	14	8
Sweating Increased	7	2
Centr. & Periph. Nerv. System Disorders		
Somnolence	13	7
Dizziness	12	7
Headache	25	23
Paresthesia	2	1
Tremor	8	2
Disorders of Skin and Appendages		
Rash	3	2
Gastrointestinal Disorders		
Anorexia	6	2
Constipation	6	4
Diarrhea/Loose Stools	20	10
Dyspepsia	8	4
Nausea	25	11
Vomiting	4	2
General		
Fatigue	12	7
Psychiatric Disorders		
Agitation	5	3
Anxiety	4	3
Insomnia	21	11
Libido Decreased	6	2
Nervousness	5	4
Special Senses		
Vision Abnormal	3	2

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=1118 ZOLOFT; N=926 placebo).
*Major depressive disorder and other premarketing controlled trials.
**Included are events reported by at least 2% of patients taking ZOLOFT except the following events, which had an incidence on placebo greater than or equal to ZOLOFT: abdominal pain, back pain, flatulence, malaise, pain, pharyngitis, respiratory disorder, upper respiratory tract infection.

Associated with Discontinuation in Placebo-Controlled Clinical Trials

Table 3 lists the adverse events associated with discontinuation of ZOLOFT (sertraline hydrochloride) treatment (incidence at least twice that for placebo and at least 1% for ZOLOFT in clinical trials) in major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD, and social anxiety disorder.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

TABLE 3
MOST COMMON ADVERSE EVENTS ASSOCIATED WITH
DISCONTINUATION IN PLACEBO-CONTROLLED CLINICAL TRIALS

Adverse Event	Major Depressive Disorder/Other*, OCD, Panic Disorder, PTSD, PMDD and Social Anxiety Disorder combined (N=2799)	Major Depressive Disorder/ Other* (N=861)	OCD (N=533)	Panic Disorder (N=430)	PTSD (N=374)	PMDD Daily Dosing (N=121)	PMDD Luteal Phase Dosing (N=136)	Social Anxiety Disorder (N=344)
Abdominal Pain	–	–	–	–	–	–	–	1%
Agitation	–	1%	–	2%	–	–	–	–
Anxiety	–	–	–	–	–	–	–	2%
Diarrhea/ Loose Stools	2%	2%	2%	1%	–	2%	–	–
Dizziness	–	–	1%	–	–	–	–	–
Dry Mouth	–	1%	–	–	–	–	–	–
Dyspepsia	–	–	–	1%	–	–	–	–
Ejaculation Failure[1]	1%	1%	1%	2%	–	N/A	N/A	2%
Fatigue	–	–	–	–	–	–	–	2%
Headache	1%	2%	–	–	1%	–	–	2%
Hot Flushes	–	–	–	–	–	–	1%	–
Insomnia	2%	1%	3%	2%	–	–	1%	3%
Nausea	3%	4%	3%	3%	2%	2%	1%	2%
Nervousness	–	–	–	–	–	2%	–	–
Palpitation	–	–	–	–	–	–	1%	–
Somnolence	1%	1%	2%	2%	–	–	–	–
Tremor	–	2%	–	–	–	–	–	–

[1]Primarily ejaculatory delay. Denominator used was for male patients only (N=271 major depressive disorder/other*; N=296 OCD; N=216 panic disorder; N=130 PTSD; No male patients in PMDD studies; N=205 social anxiety disorder).
*Major depressive disorder and other premarketing controlled trials.

Male and Female Sexual Dysfunction with SSRIs — Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 4 below displays the incidence of sexual side effects reported by at least 2% of patients taking ZOLOFT in placebo-controlled trials.

TABLE 4

Adverse Event	ZOLOFT	Placebo
Ejaculation failure* (primarily delayed ejaculation)	14%	1%
Decreased libido**	6%	1%

*Denominator used was for male patients only (N=1118 ZOLOFT; N=926 placebo)
**Denominator used was for male and female patients (N=2799 ZOLOFT; N=2394 placebo)

There are no adequate and well-controlled studies examining sexual dysfunction with sertraline treatment.

Priapism has been reported with all SSRIs.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Other Adverse Events in Pediatric Patients–**In over 600 pediatric patients treated with ZOLOFT, the overall profile of adverse events was generally similar to that seen in adult studies. However, the following adverse events, from controlled trials, not appearing in Tables 1 and 2, were reported at an incidence of at least 2% and occurred at a rate of at least twice the placebo rate (N=281 patients treated with ZOLOFT): fever, hyperkinesia, urinary incontinence, aggressive reaction, sinusitis, epistaxis, and purpura. **Other Events Observed During the Premarketing Evaluation of ZOLOFT (sertraline hydrochloride) –**Following is a list of treatment-emergent adverse events reported during premarketing assessment of ZOLOFT in clinical trials (over 4000 adult subjects) except those already listed in the previous tables or elsewhere in labeling. In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced an event of the type cited on at least one occasion while receiving ZOLOFT. All events are included except those already listed in the previous tables or elsewhere in labeling and those reported in terms so general as to be uninformative and those for which a causal relationship to ZOLOFT treatment seemed remote. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section. **Autonomic Nervous System Disorders–***Frequent:* impotence; *Infrequent:* flushing, increased saliva, cold clammy skin, mydriasis; *Rare:* pallor, glaucoma, priapism, vasodilation. **Body as a Whole–General Disorders–***Rare:* allergic reaction, allergy. **Cardiovascular–***Frequent:* palpitations, chest pain; *Infrequent:* hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder. **Central and Peripheral Nervous System Disorders–***Frequent:* hypertonia, hypoesthesia; *Infrequent:* twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare:* dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia. **Disorders of Skin and Appendages–***Infrequent:* pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare:* follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash. **Endocrine Disorders–***Rare:* exophthalmos, gynecomastia. **Gastrointestinal Disorders–***Frequent:* appetite increased; *Infrequent:* dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; *Rare:* melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration. **General–***Frequent:* back pain, asthenia, malaise, weight increase; *Infrequent:* fever, rigors, generalized edema; *Rare:* face edema, aphthous stomatitis. **Hearing and Vestibular Disorders–***Rare:* hyperacusis, labyrinthine disorder. **Hematopoietic and Lymphatic–***Rare:* anemia, anterior chamber eye hemorrhage. **Liver and Biliary System Disorders–***Rare:* abnormal hepatic function. **Metabolic and Nutritional Disorders–***Infrequent:* thirst; *Rare:* hypoglycemia, hypoglycemia reaction. **Musculoskeletal System Disorders–***Frequent:* myalgia; *Infrequent:* arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness. **Psychiatric Disorders–***Frequent:* yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent:* depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare:* withdrawal syndrome, suicide ideation, libido

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	increased, somnambulism, illusion. **Reproductive–***Infrequent:* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare:* female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis. **Respiratory System Disorders–***Frequent:* rhinitis; *Infrequent:* coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare:* hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis. **Special Senses–***Frequent:* tinnitus; *Infrequent:* conjunctivitis, earache, eye pain, abnormal accommodation; *Rare:* xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect. **Urinary System Disorders–***Infrequent:* micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; *Rare:* cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury. **Laboratory Tests–**In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT (sertraline hydrochloride) administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation. ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance. The safety profile observed with ZOLOFT treatment in patients with major depressive disorder, OCD, panic disorder, PTSD, PMDD, and social anxiety disorder is similar. **Other Events Observed During the Postmarketing Evaluation of ZOLOFT–**Reports of adverse events temporally associated with ZOLOFT that have been received since market introduction, that are not listed above and that may have no causal relationship with the drug, include the following: acute renal failure, anaphylactoid reaction, angioedema, blindness, optic neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT interval prolongation, ventricular tachycardia (including torsade de pointes-type arrhythmias), hypothyroidism, agranulocytosis, aplastic anemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, hyperglycemia, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events—clinical features (which in the majority of cases appeared to be reversible with discontinuation of ZOLOFT) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure, and death.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
EFFEXOR XR® (venlafaxine hydrochloride)	The information included in the **Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR** subsection is based on data from a pool of three 8- and 12-week controlled clinical trials in major depressive disorder (includes two U.S. trials and one European trial), on data up to 8 weeks from a pool of five controlled clinical trials in GAD with Effexor XR®, on data up to 12 weeks from a pool of two controlled clinical trials in Social Anxiety Disorder, and on data up to 12 weeks from a pool of four controlled clinical trials in panic disorder. Information on additional adverse events associated with Effexor XR in the entire development program for the formulation and with Effexor (the immediate release formulation of venlafaxine) is included in the **Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR** subsection (see also **WARNINGS** and **PRECAUTIONS**). **Adverse Findings Observed in Short-Term, Placebo-Controlled Studies with Effexor XR** Adverse Events Associated with Discontinuation of Treatment Approximately 11% of the 357 patients who received Effexor XR® (venlafaxine hydrochloride) extended-release capsules in placebo-controlled clinical trials for major depressive disorder discontinued treatment due to an adverse experience, compared with 6% of the 285 placebo-treated patients in those studies. Approximately 18% of the 1381 patients who received Effexor XR capsules in placebo-controlled clinical trials for GAD discontinued treatment due to an adverse experience, compared with 12% of the 555 placebo-treated patients in those studies. Approximately 17% of the 277 patients who received Effexor XR capsules in placebo-controlled clinical trials for Social Anxiety Disorder discontinued treatment due to an adverse experience, compared with 5% of the 274 placebo-treated patients in those studies. Approximately 7% of the 1,001 patients who received Effexor XR capsules in placebo-controlled clinical trials for panic disorder discontinued treatment due to an adverse experience, compared with 6% of the 662 placebo-treated patients in those studies. The most common events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of the Effexor XR-treated patients at a rate at least twice that of placebo for any indication) are shown in Table 3.

Table 3 Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials[1]

	Percentage of Patients Discontinuing Due to Adverse Event							
Adverse Event	Major Depressive Disorder Indication[2]		GAD Indication[3,4]		Social Anxiety Disorder Indication		Panic Disorder Indication	
	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n = 274	Effexor XR n = 1001	Placebo n = 662
Body as a Whole								
Asthenia	--	--	3%	<1%	1%	<1%	1%	0%
Headache	--	--	--	--	2%	<1%	--	--
Digestive System								
Nausea	4%	<1%	8%	<1%	4%	0%	2%	<1%
Anorexia	1%	<1%	--	--	--	--	--	--
Dry Mouth	1%	0%	2%	<1%	--	--	--	--
Vomiting	--	--	1%	<1%	--	--	--	--

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 3 Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials[1]

	Percentage of Patients Discontinuing Due to Adverse Event							
Adverse Event	Major Depressive Disorder Indication[2]		GAD Indication[3,4]		Social Anxiety Disorder Indication		Panic Disorder Indication	
	Effexor XR n = 357	Placebo n = 285	Effexor XR n = 1381	Placebo n = 555	Effexor XR n = 277	Placebo n = 274	Effexor XR n = 1001	Placebo n = 662
Nervous System								
Dizziness	2%	1%	--	--	2%	0%	--	--
Insomnia	1%	<1%	3%	<1%	3%	<1%	1%	<1%
Somnolence	2%	<1%	3%	<1%	2%	<1%	--	--
Nervousness	--	--	2%	<1%	--	--	--	--
Tremor	--	--	1%	0%	--	--	--	--
Anxiety	--	--	--	--	1%	<1%	--	--
Skin								
Sweating	--	--	2%	<1%	1%	0%	--	--
Urogenital System								
Impotence	--	--	--	--	3%[5]	0%	--	--

[1] Two of the major depressive disorder studies were flexible dose and one was fixed dose. Four of the GAD studies were fixed dose and one was flexible dose. Both of the Social Anxiety Disorder studies were flexible dose. Two of the panic disorder studies were flexible dose and two were fixed dose.
[2] In U.S. placebo-controlled trials for major depressive disorder, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 192], % Placebo [n = 202]): hypertension (1%, <1%); diarrhea (1%, 0%); paresthesia (1%, 0%); tremor (1%, 0%); abnormal vision, mostly blurred vision (1%, 0%); and abnormal, mostly delayed, ejaculation (1%, 0%).
[3] In two short-term U.S. placebo-controlled trials for GAD, the following were also common events leading to discontinuation and were considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 476]), % Placebo [n = 201]: headache (4%, <1%); vasodilatation (1%, 0%); anorexia (2%, <1%); dizziness (4%, 1%); thinking abnormal (1%, 0%); and abnormal vision (1%, 0%).
[4] In long-term placebo-controlled trials for GAD, the following was also a common event leading to discontinuation and was considered to be drug-related for Effexor XR-treated patients (% Effexor XR [n = 535], % Placebo [n = 257]): decreased libido (1%, 0%).
[5] Incidence is based on the number of men (Effexor XR = 158, placebo = 153).

Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients

Tables 4, 5, 6, and 7 enumerate the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of major depressive disorder (up to 12 weeks; dose range of 75 to 225 mg/day), of GAD (up to 8 weeks; dose range of 37.5 to 225 mg/day), of Social Anxiety Disorder (up to 12 weeks; dose range of 75 to 225 mg/day), and of panic disorder (up to 12 weeks; dose range of 37.5 to 225 mg/day), respectively, in 2% or more of patients treated with Effexor XR (venlafaxine hydrochloride) where the incidence in patients treated with Effexor XR was greater than the incidence for the respective placebo-treated patients. The table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied. Commonly Observed Adverse Events from Tables 4, 5, 6, and 7:

Major Depressive Disorder

Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	major depressive disorder indication (Table 4): Abnormal ejaculation, gastrointestinal complaints (nausea, dry mouth, and anorexia), CNS complaints (dizziness, somnolence, and abnormal dreams), and sweating. In the two U.S. placebo-controlled trials, the following additional events occurred in at least 5% of Effexor XR-treated patients (n=192) and at a rate at least twice that of the placebo group: Abnormalities of sexual function (impotence in men, anorgasmia in women, and libido decreased), gastrointestinal complaints (constipation and flatulence), CNS complaints (insomnia, nervousness, and tremor), problems of special senses (abnormal vision), cardiovascular effects (hypertension and vasodilatation), and yawning. *Generalized Anxiety Disorder* Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for all placebo-controlled trials for the GAD indication (Table 5): Abnormalities of sexual function (abnormal ejaculation and impotence), gastrointestinal complaints (nausea, dry mouth, anorexia, and constipation), problems of special senses (abnormal vision), and sweating. *Social Anxiety Disorder* Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for the 2 placebo-controlled trials for the Social Anxiety Disorder indication (Table 6): Asthenia, gastrointestinal complaints (anorexia, dry mouth, nausea), CNS complaints (anxiety, insomnia, libido decreased, nervousness, somnolence, dizziness), abnormalities of sexual function (abnormal ejaculation, orgasmic dysfunction, impotence), yawn, sweating, and abnormal vision. *Panic Disorder* Note in particular the following adverse events that occurred in at least 5% of the Effexor XR patients and at a rate at least twice that of the placebo group for 4 placebo-controlled trials for the panic disorder indication (Table 7): gastrointestinal complaints (anorexia, constipation, dry mouth), CNS complaints (somnolence, tremor), abnormalities of sexual function (abnormal ejaculation), and sweating.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 4 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Patients with Major Depressive Disorder[1,2]

	% Reporting Event	
Body System Preferred Term	**Effexor XR** (n = 357)	**Placebo** (n = 285)
Body as a Whole		
Asthenia	8%	7%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Hypertension	4%	1%
Digestive System		
Nausea	31%	12%
Constipation	8%	5%
Anorexia	8%	4%
Vomiting	4%	2%
Flatulence	4%	3%
Metabolic/Nutritional		
Weight Loss	3%	0%
Nervous System		
Dizziness	20%	9%
Somnolence	17%	8%
Insomnia	17%	11%
Dry Mouth	12%	6%
Nervousness	10%	5%
Abnormal Dreams[4]	7%	2%
Tremor	5%	2%
Depression	3%	<1%
Paresthesia	3%	1%
Libido Decreased	3%	<1%
Agitation	3%	1%

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 4 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Patients with Major Depressive Disorder[1,2]

	% Reporting Event	
Body System Preferred Term	**Effexor XR** (n = 357)	**Placebo** (n = 285)
Respiratory System		
Pharyngitis	7%	6%
Yawn	3%	0%
Skin		
Sweating	14%	3%
Special Senses		
Abnormal Vision[5]	4%	<1%
Urogenital System		
Abnormal Ejaculation (male)[6,7]	16%	<1%
Impotence[7]	4%	<1%
Anorgasmia (female)[8,9]	3%	<1%

[1] Incidence, rounded to the nearest %, for events reported by at least 2% of patients treated with Effexor XR, except the following events which had an incidence equal to or less than placebo: abdominal pain, accidental injury, anxiety, back pain, bronchitis, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, pain, palpitation, rhinitis, and sinusitis.
[2] <1% indicates an incidence greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[5] Mostly "blurred vision" and "difficulty focusing eyes."
[6] Mostly "delayed ejaculation."
[7] Incidence is based on the number of male patients.
[8] Mostly "delayed orgasm" or "anorgasmia."
[9] Incidence is based on the number of female patients.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 5 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in GAD Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n = 1381)	 Placebo (n = 555)
Body as a Whole		
Asthenia	12%	8%
Cardiovascular System		
Vasodilatation[3]	4%	2%
Digestive System		
Nausea	35%	12%
Constipation	10%	4%
Anorexia	8%	2%
Vomiting	5%	3%
Nervous System		
Dizziness	16%	11%
Dry Mouth	16%	6%
Insomnia	15%	10%
Somnolence	14%	8%
Nervousness	6%	4%
Libido Decreased	4%	2%
Tremor	4%	<1%
Abnormal Dreams[4]	3%	2%
Hypertonia	3%	2%
Paresthesia	2%	1%
Respiratory System		
Yawn	3%	<1%

Table 5 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in GAD Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n = 1381)	 Placebo (n = 555)
Skin		
Sweating	10%	3%
Special Senses		
Abnormal Vision[5]	5%	<1%
Urogenital System		
Abnormal Ejaculation[6,7]	11%	<1%
Impotence[7]	5%	<1%
Orgasmic Dysfunction (female)[8,9]	2%	0%

[1] Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, myalgia, pain, palpitation, pharyngitis, rhinitis, tinnitus, and urinary frequency.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[5] Mostly "blurred vision" and "difficulty focusing eyes."
[6] Includes "delayed ejaculation" and "anorgasmia."
[7] Percentage based on the number of males (Effexor XR = 525, placebo = 220).
[8] Includes "delayed orgasm," "abnormal orgasm," and "anorgasmia."
[9] Percentage based on the number of females (Effexor XR = 856, placebo = 335).

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 6 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Social Anxiety Disorder Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n = 277)	 Placebo (n = 274)
Body as a Whole		
Headache	34%	33%
Asthenia	17%	8%
Flu Syndrome	6%	5%
Accidental Injury	5%	3%
Abdominal Pain	4%	3%
Cardiovascular System		
Hypertension	5%	4%
Vasodilatation[3]	3%	1%
Palpitation	3%	1%
Digestive System		
Nausea	29%	9%
Anorexia[4]	20%	1%
Constipation	8%	4%
Diarrhea	6%	5%
Vomiting	3%	2%
Eructation	2%	0%
Metabolic/Nutritional		
Weight Loss	4%	0%

Table 6 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Social Anxiety Disorder Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n = 277)	 Placebo (n = 274)
Nervous System		
Insomnia	23%	7%
Dry Mouth	17%	4%
Dizziness	16%	8%
Somnolence	16%	8%
Nervousness	11%	3%
Libido Decreased	9%	<1%
Anxiety	5%	3%
Agitation	4%	1%
Tremor	4%	<1%
Abnormal Dreams[5]	4%	<1%
Paresthesia	3%	<1%
Twitching	2%	0%
Respiratory System		
Yawn	5%	<1%
Sinusitis	2%	1%
Skin		
Sweating	13%	2%
Special Senses		
Abnormal Vision[6]	6%	3%

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 6 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Social Anxiety Disorder Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n = 277)	 Placebo (n = 274)
Urogenital System		
Abnormal Ejaculation[7,8]	16%	1%
Impotence[8]	10%	1%
Orgasmic Dysfunction[9,10]	8%	0%

[1] Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: back pain, depression, dysmenorrhea, dyspepsia, infection, myalgia, pain, pharyngitis, rash, rhinitis, and upper respiratory infection.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flashes."
[4] Mostly "decreased appetite" and "loss of appetite."
[5] Mostly "vivid dreams," "nightmares," and "increased dreaming."
[6] Mostly "blurred vision."
[7] Includes "delayed ejaculation" and "anorgasmia."
[8] Percentage based on the number of males (Effexor XR = 158, placebo = 153).
[9] Includes "abnormal orgasm" and "anorgasmia."
[10] Percentage based on the number of females (Effexor XR = 119, placebo = 121).

Table 7 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Panic Disorder Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n = 1001)	 Placebo (n = 662)
Body as a Whole		
Asthenia	10%	8%
Cardiovascular System		
Hypertension	4%	3%
Vasodilatation[3]	3%	2%
Digestive System		
Nausea	21%	14%
Dry mouth	12%	6%
Constipation	9%	3%
Anorexia[4]	8%	3%
Nervous System		
Insomnia	17%	9%
Somnolence	12%	6%
Dizziness	11%	10%
Tremor	5%	2%
Libido Decreased	4%	2%

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Table 7 Treatment-Emergent Adverse Event Incidence in Short-Term Placebo-Controlled Effexor XR Clinical Trials in Panic Disorder Patients[1,2]

Body System Preferred Term	% Reporting Event Effexor XR (n = 1001)	 Placebo (n = 662)
Skin		
Sweating	10%	2%
Urogenital System		
Abnormal Ejaculation[5,6]	8%	<1%
Impotence[6]	4%	<1%
Orgasmic Dysfunction[7,8]	2%	<1%

[1] Adverse events for which the Effexor XR reporting rate was less than or equal to the placebo rate are not included. These events are: abdominal pain, abnormal vision, accidental injury, anxiety, back pain, diarrhea, dysmenorrhea, dyspepsia, flu syndrome, headache, infection, nervousness, pain, paresthesia, pharyngitis, rash, rhinitis, and vomiting.
[2] <1% means greater than zero but less than 1%.
[3] Mostly "hot flushes."
[4] Mostly "decreased appetite" and "loss of appetite."
[5] Includes "delayed or retarded ejaculation" and "anorgasmia."
[6] Percentage based on the number of males (Effexor XR = 335, placebo = 238).
[7] Includes "anorgasmia" and "delayed orgasm."
[8] Percentage based on the number of females (Effexor XR = 666, placebo = 424).

Vital Sign Changes

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled major depressive disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with 1 beat per minute for placebo. Effexor XR treatment for up to 8 weeks in premarketing placebo-controlled GAD trials was associated with a mean final on-therapy increase in pulse rate of approximately 2 beats per minute, compared with less than 1 beat per minute for placebo. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 4 beats per minute, compared with an increase of 1 beat per minute for placebo.

Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled panic disorder trials was associated with a mean final on-therapy increase in pulse rate of approximately 1 beat per minute, compared with a decrease of less than 1 beat per minute for placebo. (See the **Sustained Hypertension** section of **WARNINGS** for effects on blood pressure.)

In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean pulse was increased by about 2 beats per minute compared with a decrease of about 1 beat per minute for placebo.

Laboratory Changes

Effexor XR (venlafaxine hydrochloride) extended-release capsules treatment for up to 12 weeks in premarketing placebo-controlled trials for major depressive disorder was associated with a mean final on-therapy increase in serum cholesterol concentration of approximately 1.5 mg/dL compared with a mean final decrease of 7.4 mg/dL for placebo. Effexor XR treatment for up to 8 weeks and up to 6 months in premarketing placebo-controlled GAD trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 1.0 mg/dL and 2.3 mg/dL, respectively while placebo subjects experienced mean final decreases of 4.9 mg/dL and 7.7 mg/dL, respectively. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled Social Anxiety Disorder trials was associated with mean final on-therapy increases in serum cholesterol concentration of approximately 11.4 mg/dL compared with a mean final decrease of 2.2 mg/dL for placebo. Effexor XR treatment for up to 12 weeks in premarketing placebo-controlled panic disorder trials was associated with mean final on-therapy increases in serum cholesterol

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	concentration of approximately 5.8 mg/dL compared with a mean final decrease of 3.7 mg/dL for placebo. Patients treated with Effexor tablets (the immediate-release form of venlafaxine) for at least 3 months in placebo-controlled 12-month extension trials had a mean final on-therapy increase in total cholesterol of 9.1 mg/dL compared with a decrease of 7.1 mg/dL among placebo-treated patients. This increase was duration dependent over the study period and tended to be greater with higher doses. Clinically relevant increases in serum cholesterol, defined as 1) a final on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, or 2) an average on-therapy increase in serum cholesterol ≥50 mg/dL from baseline and to a value ≥261 mg/dL, were recorded in 5.3% of venlafaxine-treated patients and 0.0% of placebo-treated patients (see **PRECAUTIONS-General-Serum Cholesterol Elevation**). **ECG Changes** In a flexible-dose study, with Effexor doses in the range of 200 to 375 mg/day and mean dose greater than 300 mg/day, the mean change in heart rate was 8.5 beats per minute compared with 1.7 beats per minute for placebo. (See the Use in Patients with Concomitant Illness section of **PRECAUTIONS**.) **Other Adverse Events Observed During the Premarketing Evaluation of Effexor and Effexor XR** During its premarketing assessment, multiple doses of Effexor XR were administered to 705 patients in Phase 3 major depressive disorder studies and Effexor was administered to 96 patients. During its premarketing assessment, multiple doses of Effexor XR were also administered to 1381 patients in Phase 3 GAD studies, 277 patients in Phase 3 Social Anxiety Disorder studies, and 1314 patients in Phase 3 panic disorder studies. In addition, in premarketing assessment of Effexor, multiple doses were administered to 2897 patients in Phase 2 to Phase 3 studies for major depressive disorder. The conditions and duration of exposure to venlafaxine in both development programs varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient (Effexor only) and outpatient studies, fixed-dose, and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 6670 patients exposed to multiple doses of either formulation of venlafaxine who experienced an event of the type cited on at least one occasion while receiving venlafaxine. All reported events are included except those already listed in Tables 4, 5, 6, and 7 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with venlafaxine, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency using the following definitions: **frequent** adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients. Body as a whole - **Frequent:** chest pain substernal, chills, fever, neck pain; **Infrequent:** face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; **Rare:** appendicitis, bacteremia, carcinoma, cellulitis. Cardiovascular system - **Frequent:** migraine, postural hypotension, tachycardia; **Infrequent:** angina pectoris, arrhythmia, bradycardia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; **Rare:** aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. Digestive system - **Frequent:** increased appetite; **Infrequent:** bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; **Rare:** abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage,

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. Endocrine system - **Rare:** galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. Hemic and lymphatic system - **Frequent:** ecchymosis; **Infrequent:** anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; **Rare:** basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. Metabolic and nutritional - **Frequent:** edema, weight gain; **Infrequent:** alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT (AST) increased, SGPT (ALT) increased, thirst; **Rare:** alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. Musculoskeletal system - **Frequent:** arthralgia; **Infrequent:** arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; **Rare:** bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. Nervous system - **Frequent:** amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; **Infrequent:** akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; **Rare:** abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barre Syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. Respiratory system - **Frequent:** cough increased, dyspnea; **Infrequent:** asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; **Rare:** atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. Skin and appendages - **Frequent:** pruritus; **Infrequent:** acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; **Rare:** brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. Special senses - **Frequent:** abnormality of accommodation, mydriasis, taste perversion; **Infrequent:** conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. Urogenital system - **Frequent:** prostatic disorder (prostatitis, enlarged prostate, and prostate irritability),* urination impaired; **Infrequent:** albuminuria, amenorrhea,* cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea,* menorrhagia,* metrorrhagia,* nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage,* vaginitis*; **Rare:** abortion,* anuria, breast discharge, breast engorgement, balanitis,* breast enlargement, endometriosis,* female lactation,* fibrocystic breast, calcium crystalluria, cervicitis,* orchitis,* ovarian cyst,* bladder pain, prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm,* vaginal dryness.* * Based on the number of men and women as appropriate. **Postmarketing Reports** Voluntary reports of other adverse events temporally associated with the use of venlafaxine that have been received since market introduction and that may have no causal relationship with the use of venlafaxine include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, impaired coordination and balance, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	of ventricular fibrillation and ventricular tachycardia, including torsade de pointes; epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease, involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly). There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
Anafranil® (clomipramine hydrochloride)	**Commonly Observed** The most commonly observed adverse events associated with the use of Anafranil and not seen at an equivalent incidence among placebo-treated patients were gastrointestinal complaints, including dry mouth, constipation, nausea, dyspepsia, and anorexia; nervous system complaints, including somnolence, tremor, dizziness, nervousness, and myoclonus; genitourinary complaints, including changed libido, ejaculatory failure, impotence, and micturition disorder; and other miscellaneous complaints, including fatigue, sweating, increased appetite, weight gain, and visual changes. **Leading to Discontinuation of Treatment** Approximately 20% of 3616 patients who received Anafranil in U.S. premarketing clinical trials discontinued treatment because of an adverse event. Approximately one-half of the patients who discontinued (9% of the total) had multiple complaints, none of which could be classified as primary. Where a primary reason for discontinuation could be identified, most patients discontinued because of nervous system complaints (5.4%), primarily somnolence. The second-most-frequent reason for discontinuation was digestive system complaints (1.3%), primarily vomiting and nausea. There was no apparent relationship between the adverse events and elevated plasma drug concentrations. **Incidence in Controlled Clinical Trials** The following table enumerates adverse events that occurred at an incidence of 1% or greater among patients with OCD who received Anafranil in adult or pediatric placebo-controlled clinical trials. The frequencies were obtained from pooled data of clinical trials involving either adults receiving Anafranil (N=322) or placebo (N=319) or children treated with Anafranil (N=46) or placebo (N=44). The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the populations studied.

Incidence of Treatment-Emergent Adverse Experience in Placebo-Controlled Trials (Percentage of Patients Reporting Event)

Body System/ Adverse Event*	Adults		Children	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
Nervous System				
Somnolence	54	16	46	11
Tremor	54	2	33	2
Dizziness	54	14	41	14
Headache	52	41	28	34
Insomnia	25	15	11	7
Libido change	21	3	_	_
Nervousness	18	2	4	2
Myoclonus	13	_	2	_
Increased appetite	11	2	_	2
Paresthesia	9	3	2	2
Anxiety	9	4	2	_
Twitching	7	1	4	5
Impaired concentration	5	2	_	_
Depression	5	1	_	_

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Body System/ Adverse Event*	Adults		Children	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
Hypertonia	4	1	2	_
Sleep disorder	4	_	9	5
Psychosomatic disorder	3	_	_	_
Yawning	3	_	_	_
Confusion	3	_	2	_
Speech disorder	3	_	_	_
Abnormal dreaming	3	_	_	2
Agitation	3	_	_	_
Migraine	3	_	_	_
Depersonalization	2	_	2	_
Irritability	2	2	2	_
Emotional lability	2	_	_	2
Panic reaction	1	_	2	_
Aggressive reaction	_	_	2	_
Paresis	_	_	2	_
Skin and Appendage				
Increased sweating	29	3	9	_
Rash	8	1	4	2
Pruritus	6	_	2	2
Dermatitis	2	_	_	2
Acne	2	2	_	5
Dry skin	2	_	_	5
Urticaria	1	_	_	_
Abnormal skin color	_	_	2	_
Digestive System				
Dry mouth	84	17	63	16
Constipation	47	11	22	9
Nausea	33	14	9	11
Dyspepsia	22	10	13	2
Diarrhea	13	9	7	5
Anorexia	12	_	22	2
Abdominal pain	11	9	13	16
Vomiting	7	2	7	_
Flatulence	6	3	_	2

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Body System/ Adverse Event*	Adults		Children	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
Tooth disorder	5	_	_	_
Gastrointestinal disorder	2	_	_	2
Dysphagia	2	_	_	_
Esophagitis	1	_	_	_
Eructation	_	_	2	2
Ulcerative Stomatitis	_	_	2	_
Body as a Whole				
Fatigue	39	18	35	9
Weight increase	18	1	2	_
Flushing	8	_	7	_
Hot flushes	5	_	2	_
Chest pain	4	4	7	_
Fever	4	_	2	7
Allergy	3	3	7	5
Pain	3	2	4	2
Local edema	2	4	_	_
Chills	2	1	_	_
Weight decrease	_	_	7	_
Otitis media	_	_	4	5
Asthenia	_	_	2	_
Halitosis	_	_	2	_
Cardiovascular System				
Postural hypotension	6	_	4	_
Palpitation	4	2	4	_
Tachycardia	4	_	2	_
Syncope	_	_	2	_
Respiratory System				
Pharyngitis	14	9	_	5
Rhinitis	12	10	7	9
Sinusitis	6	4	2	5
Coughing	6	6	4	5
Dyspnea	_	_	2	_
Laryngitis	_	1	2	_

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS				
	Body System/ Adverse Event*	Adults		Children	
		Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
	Urogenital System Male and Female Patients Combined				
	Micturition disorder	14	2	4	2
	Urinary tract infection	6	1	_	_
	Micturition frequency	5	3	_	_
	Urinary retention	2	_	7	_
	Dysuria	2	2	_	_
	Cystitis	2	_	_	_
	Female Patients Only	(N=182)	(N=167)	(N=10)	(N=21)
	Dysmenorrhea	12	14	10	10
	Lactation (nonpuerperal)	4	_	_	_
	Menstrual disorder	4	2	_	_
	Vaginitis	2	_	_	_
	Leukorrhea	2	_	_	_
	Breast enlargement	2	_	_	_
	Breast pain	1	_	_	_
	Amenorrhea	1	_	_	_
	Male Patients Only	(N=140)	(N=152)	(N=36)	(N=23)
	Ejaculation failure	42	2	6	_
	Impotence	20	3	_	_
	Special Senses				
	Abnormal vision	18	4	7	2
	Taste perversion	8	_	4	_
	Tinnitus	6	_	4	_
	Abnormal lacrimation	3	2	_	_
	Mydriasis	2	_	_	_
	Conjunctivitis	1	_	_	_
	Anisocoria	_	_	2	_
	Blepharospasm	_	_	2	_
	Ocular allergy	_	_	2	_
	Vestibular disorder	_	_	2	2
	Musculoskeletal				
	Myalgia	13	9	_	_
	Back pain	6	6	_	_

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS

Body System/ Adverse Event*	Adults		Children	
	Anafranil (N=322)	Placebo (N=319)	Anafranil (N=46)	Placebo (N=44)
Arthralgia	3	5	_	_
Muscle weakness	1	_	2	_
Hemic and Lymphatic				
Purpura	3	_	_	_
Anemia	_	_	2	2
Metabolic and Nutritional				
Thirst	2	2	_	2

***Events reported by at least 1% of Anafranil patients are included.**

Other Events Observed During the Premarketing Evaluation of Anafranil

During clinical testing in the U.S., multiple doses of Anafranil® (clomipramine hydrochloride capsules USP) were administered to approximately 3600 subjects. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that follow, a modified World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 3525 individuals exposed to Anafranil who experienced an event of the type cited on at least one occasion while receiving Anafranil. All events are included except those already listed in the previous table, those reported in terms so general as to be uninformative, and those in which an association with the drug was remote. It is important to emphasize that although the events reported occurred during treatment with Anafranil, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole – *Infrequent* - general edema, increased susceptibility to infection, malaise. *Rare* - dependent edema, withdrawal syndrome.

Cardiovascular System – *Infrequent* - abnormal ECG, arrhythmia, bradycardia, cardiac arrest, extrasystoles, pallor. *Rare* - aneurysm, atrial flutter, bundle branch block, cardiac failure, cerebral hemorrhage, heart block, myocardial infarction, myocardial ischemia, peripheral ischemia, thrombophlebitis, vasospasm, ventricular tachycardia.

Digestive System – *Infrequent* - abnormal hepatic function, blood in stool, colitis, duodenitis, gastric ulcer, gastritis, gastroesophageal reflux, gingivitis, glossitis, hemorrhoids, hepatitis, increased saliva, irritable bowel syndrome, peptic ulcer, rectal hemorrhage, tongue ulceration, tooth caries. *Rare* - cheilitis, chronic enteritis, discolored feces, gastric dilatation, gingival bleeding, hiccup, intestinal obstruction, oral/pharyngeal edema, paralytic ileus, salivary gland enlargement.

Endocrine System – *Infrequent* - hypothyroidism. *Rare* - goiter, gynecomastia, hyperthyroidism.

Hemic and Lymphatic System – *Infrequent* - lymphadenopathy. *Rare* - leukemoid reaction, lymphoma-like disorder, marrow depression.

Metabolic and Nutritional Disorder – *Infrequent* - dehydration, diabetes mellitus, gout, hypercholesterolemia, hyperglycemia, hyperuricemia, hypokalemia. *Rare* - fat intolerance, glycosuria.

Musculoskeletal System – *Infrequent* - arthrosis. *Rare* - dystonia, exostosis, lupus erythematosus rash, bruising, myopathy, myositis, polyarteritis nodosa, torticollis.

Nervous System – *Frequent* - abnormal thinking, vertigo. *Infrequent* - abnormal coordination, abnormal EEG, abnormal gait, apathy, ataxia, coma, convulsions, delirium, delusion, dyskinesia, dysphonia, encephalopathy, euphoria, extrapyramidal disorder, hallucinations, hostility, hyperkinesia, hypnagogic hallucinations, hypokinesia, leg cramps, manic reaction, neuralgia, paranoia, phobic disorder, psychosis, sensory disturbance, somnambulism, stimulation, suicidal

TABLE 25. ADVERSE EVENTS – CONTINUED

BRAND	ADVERSE EVENTS
	ideation, suicide attempt, teeth-grinding. *Rare* - anticholinergic syndrome, aphasia, apraxia, catalepsy, cholinergic syndrome, choreoathetosis, generalized spasm, hemiparesis, hyperesthesia, hyperreflexia, hypoesthesia, illusion, impaired impulse control, indecisiveness, mutism, neuropathy, nystagmus, oculogyric crisis, oculomotor nerve paralysis, schizophrenic reaction, stupor, suicide. **Respiratory System –** *Infrequent* - bronchitis, hyperventilation, increased sputum, pneumonia. *Rare* - cyanosis, hemoptysis, hypoventilation, laryngismus. **Skin and Appendages –** *Infrequent* - alopecia, cellulitis, cyst, eczema, erythematous rash, genital pruritus, maculopapular rash, photosensitivity reaction, psoriasis, pustular rash, skin discoloration. *Rare* - chloasma, folliculitis, hypertrichosis, piloerection, seborrhea, skin hypertrophy, skin ulceration. **Special Senses –** *Infrequent* - abnormal accommodation, deafness, diplopia, earache, eye pain, foreign body sensation, hyperacusis, parosmia, photophobia, scleritis, taste loss. *Rare* - blepharitis, chromatopsia, conjunctival hemorrhage, exophthalmos, glaucoma, keratitis, labyrinth disorder, night blindness, retinal disorder, strabismus, visual field defect. **Urogenital System –** *Infrequent* - endometriosis, epididymitis, hematuria, nocturia, oliguria, ovarian cyst, perineal pain, polyuria, prostatic disorder, renal calculus, renal pain, urethral disorder, urinary incontinence, uterine hemorrhage, vaginal hemorrhage. *Rare* - albuminuria, anorgasmy, breast engorgement, breast fibroadenosis, cervical dysplasia, endometrial hyperplasia, premature ejaculation, pyelonephritis, pyuria, renal cyst, uterine inflammation, vulvar disorder.

INTRODUCTION TO OBSESSIVE COMPULSIVE DISORDER

CLINICAL FEATURES AND DIAGNOSTIC CRITERIA

OCD is defined by the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) as an anxiety disorder characterized by the presence of obsessions (recurrent and persistent thoughts, impulses, or images) and/or compulsions (repetitive behaviors or mental acts that the person feels driven to perform), which a) the person recognizes as unreasonable or excessive, b) cause marked distress, c) interfere with normal activities, and d) are time consuming (consume >1 hour per day).[2] Complete diagnostic criteria are shown in Table 26 and common obsessions and compulsions are shown in Table 27.

TABLE 26. DSM-IV CRITERIA FOR OCD

A. Either Obsessions or Compulsions

Obsessions as defined by (1), (2), (3), and (4):

(1) Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress.

(2) The thoughts, impulses, or images are not simply excessive worries about real-life problems.

(3) The person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action.

(4) The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion).

Compulsions as defined by (1) and (2):

(1) Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly.

(2) The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive.

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. Note: This does not apply to children.

C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an Eating Disorder; hair pulling in the presence of Trichotillomania; concern with appearance in the presence of Body Dysmorphic Disorder; preoccupation with drugs in the presence of a Substance Use Disorder; preoccupation with having a serious illness in the presence of Hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a Paraphilia; or guilty ruminations in the presence of Major Depressive Disorder).

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify if:

With Poor Insight: If, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable.

TABLE 27. COMMON OBSESSIONS AND COMPULSIONS

Common Obsessions
Symmetry, Order, Exactness, and "Just Right" Obsessions • Need for symmetry or exactness in dressing or grooming. • Fear of saying the wrong thing or not saying it "just right"
Contamination Obsessions • Concern with dirt or germs. • Concern or disgust with bodily waste or secretions (e.g., urine, feces or saliva). • Concerned with having an illness or disease.
Safety, Harm, and Violent Obsessions • Fear of harm due to carelessness. • Fear might harm self on impulse. • Fear might harm others because not careful enough. • Violent or horrific images.
Hoarding/Saving Obsessions • Need to hoard or save things. • Fear of losing objects or information.
Other Obsessions • Fear of losing things. • Fear of not saying just the right thing. • Lucky/unlucky numbers.
Common Compulsions
• Cleaning and grooming, such as washing hands, showering or brushing teeth over and over again. • Checking drawers, door locks, and appliances to be sure they are shut, locked or turned off. • Repeating, such as going in and out of a door, sitting down and getting up from a chair, or touching certain objects several times. • Ordering and arranging items in certain ways. • Counting over and over to a certain number. • Saving newspapers, mail, or containers when they are no longer needed. • Seeking constant reassurance and approval. Adapted from the Yale-Brown Obsessive-Compulsive Scale Checklist[40]

In 1952, DSM-I classified OCD as "obsessive compulsive reaction;" as such, the disorder was defined as "anxiety associated with the persistence of unwanted ideas and repetitive impulses to perform acts which may be considered morbid by the patient."[41] In 1980, with the publication of DSM-III, the disorder was given its current designation as "obsessive compulsive disorder."[42]

EPIDEMIOLOGY

Obsessive compulsive disorder is a relatively rare psychiatric disorder. Population-based estimates of the lifetime prevalence of OCD in the United States (U.S.), based on the Epidemiologic Catchment Area (ECA) study[43] and the National Comorbidity Survey (NCS),[3] range from 1% to 3%. Most recently, the estimate of the lifetime prevalence of OCD is 1.6%.[3] Because many people with OCD are never diagnosed and treated, the reported prevalence of OCD in managed-care populations is dramatically smaller. In a study of 1.7 million adult Northern California Kaiser Permanente HMO members, the 1-year prevalence of clinically-recognized OCD (1995–1996) was 0.084%, or 84 in 100,000 patients.[18]

Obsessive compulsive disorder occurs about equally in men and women, with a slight preponderance in women.[44] The mean age of onset of OCD is between 21.9 and 35.5 years,[4] with only 15% of persons with obsessions developing OCD after age 35.[45] Men tend to have an earlier age of onset than women.[44]

PATHOGENESIS

Evidence suggests that both heredity and environment contribute to the development of OCD. Family members of those with OCD are 5 to 7 times more likely to be diagnosed with OCD than family members of those without OCD.[46-48] Prevalence among twins is reported to range from 27%–65%.[49]

Research indicates that serotonergic and dopaminergic systems may be implicated in the pathogenesis and maintenance of OCD.[50] Functional neuroimaging findings demonstrate abnormal activity in the orbital frontal cortex, the anterior cingulate, dorsolateral prefrontal cortex, caudate nucleus, and thalamus in patients with OCD.[50]

COMORBID PSYCHIATRIC ILLNESS

Patients diagnosed with any psychiatric illness have a high likelihood of being diagnosed with comorbid psychiatric illnesses;[19] OCD is no exception. Among 334 patients seeking outpatient care for OCD, 92% met criteria for at least 1 additional psychiatric condition; the mean number of psychiatric comorbidities among this sample of patients with OCD was 2.88 (SD=1.96).[51]

Data from the ECA study[43] and an Australian national study[52] indicated that up to 60% of persons who satisfied criteria for OCD had comorbid mental disorders; in these studies, comorbid major depression, anxiety disorders, and alcohol/substance abuse were commonly seen in conjunction with OCD.

CLINICAL PRESENTATION

A defining characteristic of OCD is that afflicted individuals usually recognize that their obsessions and/or compulsions are unreasonable and excessive.[2] As a result, those with OCD are commonly distressed and embarrassed by their symptoms.[2] Consequently, many people with OCD hesitate to disclose OCD-related symptoms to their physician.[16] Common presenting complaints of patients with OCD include relationship problems, stress, alcohol/drug problems, mood disorders, and anxiety and nervousness.[44]

Given the reticence toward disclosure of OCD symptoms and the hesitation to disclose them to their doctor, only 1 in 3 persons with OCD admit to having discussed their disorder with a physician.[19] In a survey of 8,580 UK residents, 62% of those who met criteria for current OCD reported that they had talked with a physician about “emotional problems” but had not disclosed their OCD symptoms.[16]

The portal for entry to OCD care may more frequently occur at the outpatient medical (rather than mental health) setting. Those with OCD may experience heightened concerns about contamination or illness, which may drive them to seek medical care.[2] Washing rituals and compulsive skin picking may cause skin problems, leading patients with OCD to consult dermatologists.[24] In fact, studies of patients attending dermatology clinics have found that 20% to 25% satisfy criteria for a current diagnosis of OCD.[24, 25] In one study, among dermatology patients meeting OCD diagnostic criteria, 94% had not been previously diagnosed with OCD.[25]

COURSE OF ILLNESS

Persons with OCD typically experience a chronic waxing and waning course with exacerbations associated with stress.[2] About 15% show a progressive deterioration in social and occupational functioning.[2] Only 5% have an episodic course with minimal or no symptoms between episodes.[2]

In a 40-year follow-up study of 251 patients diagnosed with OCD, 83% of patients had improved, but only 20% had completely recovered from OCD.[5] In a two-site prospective longitudinal study of adult patients with OCD, data were collected on the course of illness in 77 patients for 2 years.[53] The probability of achieving total remission during the 2-year period was 12%, and the probability of partial remission was 47%. In another prospective study, 100 clinic patients with OCD were followed for up to 5 years after intake.[6] The probability of full remission for at least a 2-month period was 22% at 5 years, and the probability of partial remission was 53%. Significant predictors of partial remission included

being married and having lower global severity scores at intake. Although the likelihood of receiving an SSRI was associated with worse outcome in this study, investigators judged this association as spurious, since poorly functioning patients were more likely to have received an SSRI.

OCD IS UNDER-DETECTED AND UNDER-TREATED

Under-detection. Individuals with OCD often experience long delays between the onset of symptoms and initiation of treatment. There was a reported 10-year lag between onset of symptoms and seeking help, a 6-year lag between seeking help and receiving a correct diagnosis, and a 1.5-year lag between receiving a correct diagnosis and obtaining appropriate treatment.[11] Thus, in total, there was a reported 17-year delay between onset of OCD symptoms and receipt of appropriate treatment. In a more recent study, 293 surveyed patients with OCD reported a mean of more than 11 years between the full onset of symptoms and receipt of treatment.[20]

Under-treatment. Once identified, OCD is frequently inappropriately or inadequately treated. Thirty-five percent of surveyed respondents with OCD, who were members of the OCD Foundation, reported having been inappropriately treated due to either receiving an incorrect diagnosis or an inappropriate medication (drugs other than a serotonin reuptake inhibitor [SRI]).[11]

Among newly-diagnosed patients with OCD enrolled in an HMO, less than half (42.8%) were prescribed adequate pharmacotherapy (defined as ≥8 weeks of an SRI at therapeutic daily doses) at least once in the 12 months following their first visit for OCD.[28]

In analysis of a survey of U.S. psychiatrists regarding the treatment of 123 patients with OCD, patients were classified as having received either cognitive-behavioral therapy (CBT), high-intensity SRI therapy ("high intensity" referred to higher doses of SRIs), or both CBT and high-intensity SRI therapy. Although 65% of patients had received an SRI, only 39.4% had received SRIs at a dose believed to be effective for the treatment of OCD ("high intensity" SRI); 7.5% had received CBT alone; and 53.1% had received neither CBT nor high-intensity SRI therapy.[30]

In a study of 313 adults in The Netherlands who were seeking outpatient treatment for OCD, only 49% had received a first-line SRI indicated for OCD.[31] Among all 313 treated patients, 19.5% (61) received an ineffective dose (15% received a minimally effective dose). Using the lowest effective dose as the criterion, 29.6% of all treated patients had received adequate pharmacotherapy.

In a retrospective analysis over 9 years (1997-2006), investigators examined adequacy and appropriateness of pharmacotherapy among Florida Medicaid-enrolled adults newly diagnosed with OCD.[29] Adequate pharmacotherapy was defined as at least 12 consecutive weeks of SSRI treatment and an average daily SSRI dose (excluding the first 6 weeks of psychotropic use where titration was likely) within the target range specified by recent American Psychiatric Association (APA) guidelines.[54] Among the 987 patients who were prescribed SSRIs, only 25% received adequate pharmacotherapy during the study period. Specifically, 23% received less than 12 weeks of an SSRI, and 77% received SSRI doses below the minimum guideline-recommended target range.[54]

Given that the portal of entry for OCD may occur in the primary care setting, PCPs may be well placed to identify persons with OCD by inquiring directly about symptoms.[17] The National Institute for Health and Clinical Excellence (NICE) recommends that active enquiry, including questions from the 5-item Zohar-Fineberg Obsessive Compulsive Screen (ZF-OCS), be incorporated into every patient mental-state examination (Table 28).[17] The ZF-OCS was designed to be administered by a nurse or physician and requires less than 1 minute to complete.[17] The instrument was validated against the Mini International Neuropsychiatric Interview in a small study of UK dermatology clinic outpatients, where it was found to have good patient acceptance as well as satisfactory sensitivity (94.4%) and specificity (85.1%).[25] Additional larger studies are needed to ensure the reliability and validity of this screening instrument in primary care samples.

TABLE 28. ZOHAR-FINEBERG OBSESSIVE COMPULSIVE SCREEN

1. Do you wash or clean a lot?
2. Do you check things a lot?
3. Is there any thought that keeps bothering you that you would like to get rid of but can't?
4. Do your daily activities take a long time to finish?
5. Are you concerned about orderliness or symmetry?

BURDEN OF OCD

Impact of OCD on Functioning and Quality of Life

Obsessive compulsive disorder ranks among the most disabling of psychiatric and medical disorders. In 1990, the World Health Organization rated OCD among the 10 most disabling conditions and estimated that the disorder accounted for 2.2% of total disability worldwide.[7]

One in four of those with OCD report having previously attempted suicide,[8] a rate twice that of persons with other types of anxiety and depressive disorders (25.7% versus 14.5%, p=0.005) and over 11 times that seen among those without psychiatric conditions (25.7% versus 2.3%, p<0.001).[8]

Individuals with OCD often suffer from marked impairment in virtually every domain of quality of life and psychosocial functioning, including the ability to work and perform household duties, subjective sense of well-being, social relationships, and the ability to enjoy leisure activities.[10] Regarding occupational functioning, one third of adults with OCD are unable to work due to their mental illness.[10] Over a lifetime, persons with OCD lose about 3 years of wages, on average.[11]

Social relationships are substantially impaired among those with OCD, who are significantly less likely to be married or cohabiting than persons with other types of anxiety or depressive disorders.[8] In a study comparing day hospital patients with OCD to age- and gender-matched schizophrenic day hospital patients, investigators found that both groups reported similar impairment in social functioning and living skills at intake (although patients with OCD showed greater improvement at discharge).[9]

Impact of OCD on the Family

Obsessive compulsive disorder also negatively affects family members. Several studies indicate that family members commonly accommodate to the person with the disorder by participating in various compulsive behaviors.[13-15] For example, family members may succumb to demands that shoes be perfectly lined up at the front door in order of their size, or that members disinfect their hands prior to entering the house in order to avoid contaminating the household. Eighty-two percent of family members of OCD-afflicted individuals report some disruption in personal and social activities, and more than 60% report marital discord, loss of leisure, and financial problems.[13] One study found that relatives of patients with OCD were more likely to report crying and depressive symptoms than were relatives of patients with depression (84% versus 61%, respectively, p<0.02).[12]

Impact of OCD on Healthcare Utilization

Psychiatric Services. One quarter of patients with OCD report having been hospitalized at least once in their lifetime due to the disorder.[11] Rates of inpatient psychiatric hospitalization are 3 times higher than those for patients with generalized anxiety disorder, depressive episode, phobias, panic disorder, or mixed anxiety and depressive disorder.[16]

Medical Services Use. Persons with anxiety disorders, including OCD, tend to be disproportionately high utilizers of medical services.[23, 55] As previously noted, a study among HMO members revealed that those with OCD had 63% higher mean costs for nonpsychiatric visits and 56% higher costs for laboratory and radiology services compared with patients without psychiatric diagnoses.[22]

There is evidence that patients with OCD more frequently visit cardiologists and dermatologists, compared with patients with other anxiety disorders.[23] A multi-site study in Canada revealed that, compared to patients with other anxiety disorders, those with OCD were significantly more likely to be high utilizers (defined as 10 or more consultations in the previous year) of mental health services (OR 3.78, 95% CI 1.23-11.58).[56] Similar findings were reported among respondents of a United Kingdom survey in which persons with OCD were twice as likely to receive mental health treatment (40% versus 23%; p<0.001), and more than 3 times as likely to have been hospitalized for mental health treatment during their lifetime (20% versus 6%, p<0.001), compared to those with other anxiety disorders or depression.[16]

In a matched comparison of Florida Medicaid adult patients with pure OCD (OCD without comorbid depression, bipolar disorder, or psychoses) and patients with pure depression (depression without comorbid OCD, bipolar disorder, or psychoses), those with pure OCD had an approximately 2 times greater 2-year, median, per-patient total (inpatient, outpatient, and pharmacy) number of healthcare claims (126.0 versus 68.4, p<0.0001) and 3 times higher total costs ($25,666 versus $7,732, p<0.0001) than those with pure depression.[27] Much of the difference in healthcare utilization between these groups was accounted for by a 65% greater median number of outpatient visits for medical treatment among those with pure OCD versus pure depression (86.0 versus 56.0, p=0.0007), which resulted in approximately 2 times greater median total medical costs for outpatient visits for those with pure OCD than their counterparts with pure depression.

Economic Burden of OCD

Because OCD is frequently under-recognized and under-treated, the disorder exacts a high economic burden on the healthcare system and society. A 1990 analysis of ECA findings estimated the total cost of OCD at $8.4 billion ($13.3 billion in 2007 dollars).[A,57] Direct medical costs were estimated at $2.1 billion ($3.3 billion in 2007 dollars) and indirect costs (lost productivity and premature death due to suicide) were estimated at $6.2 billion ($9.8 billion in 2007 dollars).

To examine the cost of inappropriate treatment of patients with OCD, Hollander compared the annual cost of patients with OCD who received appropriate treatment (defined as receiving an SRI or behavioral therapy) to those who received inappropriate treatment (35% of the sample).[11] The 6-month cost for provider fees among those receiving inappropriate pharmacotherapy was $2,811 versus $1,958 (p<0.05) for those receiving appropriate pharmacotherapy (both in 2007 dollars).[11] The total yearly cost of inappropriate treatment for all individuals with OCD was estimated at $2.4 billion ($3.8 billion in 2007 dollars).

[A] Cost updated using Consumer Price Index.

PLACE OF LUVOX® CR IN THE TREATMENT OF OCD

Fluvoxamine, long recognized as an effective pharmacologic treatment for OCD,[58] is a first-line, guideline-recommended pharmacologic treatment for OCD.[54]

However, prior to the FDA approval of LUVOX® CR, fluvoxamine was only available as an immediate-release capsule administered twice daily. LUVOX® CR is specifically formulated to minimize peak to trough fluvoxamine levels over 24 hours compared to fluvoxamine IR, and may offer the potential for lower incidence of peak-related adverse events.

Five crossover studies of over 60 individuals evaluated LUVOX® CR formulation prototypes based on rates of dissolution delivery. The slow dissolution delivery prototype successfully fulfilled all of the PK targets.

LUVOX® CR uses the SODAS® (Spheroidal Oral Drug Absorption System) multiparticulate drug delivery system developed by Elan Pharmaceuticals.[59] Each LUVOX® CR capsule contains immediate-release and extended-release beads.[59] The extended-release beads are uniform spherical beads 1-2 mm in diameter containing fluvoxamine plus excipients and coated with product-specific controlled release polymers.[59] Extended release is achieved when, over 4 hours, the soluble polymers dissolve, leaving pores within the outer membrane.[59] Fluid then enters the core of the beads and dissolves the fluvoxamine.[59] This provides a second release of the drug.[59]

Compared to IR fluvoxamine, LUVOX® CR provides:

- Lower and later peak concentrations of fluvoxamine
- C_{max} <85%, with relative time to peak concentration delayed by >3 hours[59]
- Higher trough concentrations
  - C_{24h} >110%[59]
- Similar bioavailability
  - AUC >80%.[59]

INDICATIONS FOR TREATMENT

Treatment for OCD is indicated when patients meet DSM-IV criteria for OCD and symptoms interfere with functioning or cause significant distress.[54]

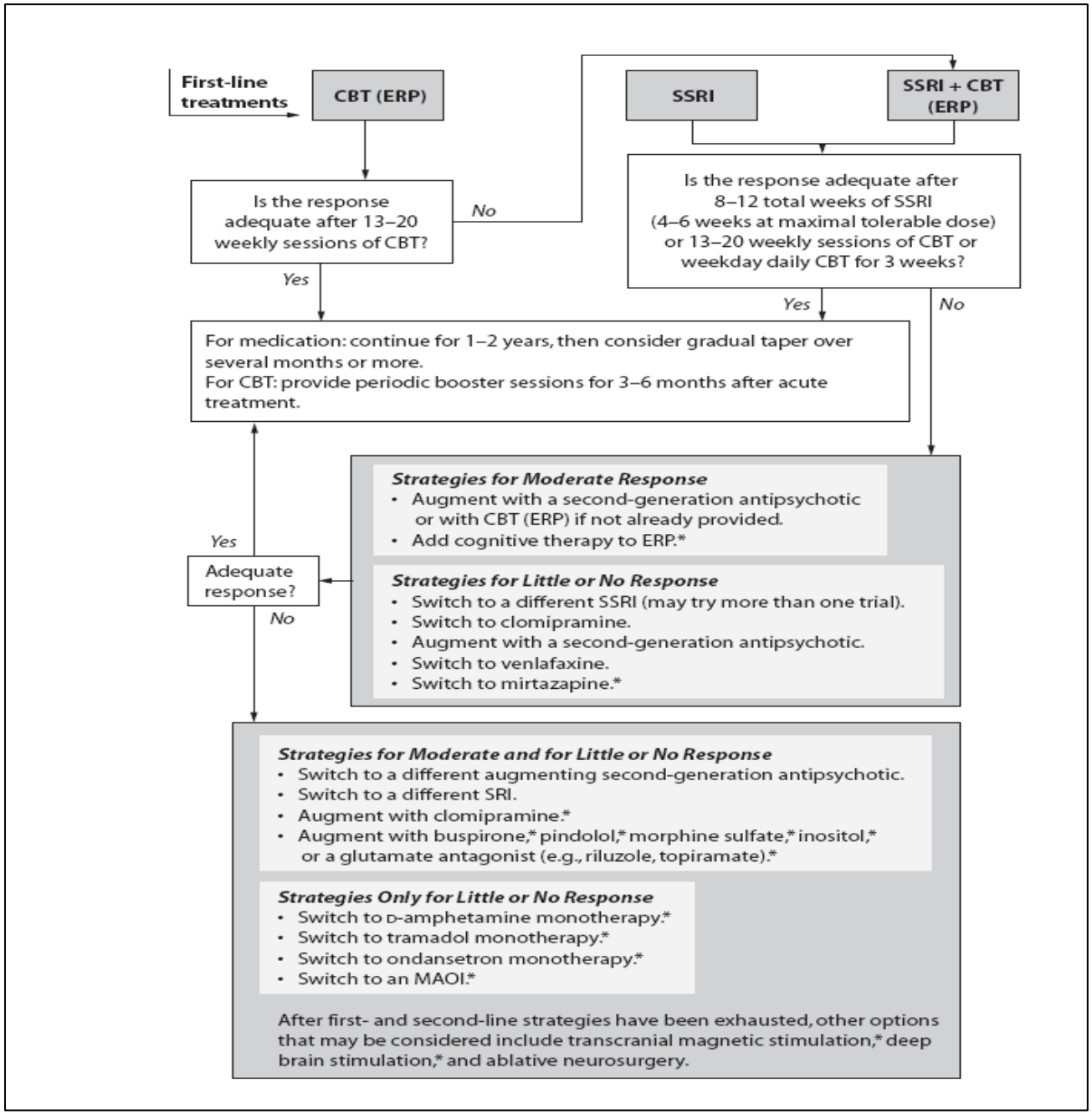
GOALS OF TREATMENT

The goals of OCD treatment include decreasing symptom frequency and severity, and improving the patient's functioning and quality of life.[54] Treatment goals also include enhancing the patient's ability to cooperate with care despite the frightening cognitions that are typical of OCD, anticipating stressors likely to exacerbate the condition and helping the patient develop coping strategies, providing assistance and support in dealing with stresses, monitoring the patient's psychiatric status and intervening as indicated, minimizing any adverse effects of treatment (e.g., medication side effects), and educating the patient and family regarding the disorder and its treatment.[54] Reasonable treatment outcome targets include less than 1 hour per day spent obsessing and performing compulsive behaviors, no more than mild OCD-related anxiety, an ability to live with uncertainty, and little or no interference of OCD with the tasks of ordinary living.[54]

TREATMENT OPTIONS

In 2007, the APA published practice guidelines for the treatment of OCD.[54] Figure 1 shows the algorithm for determining the sequence of treatments in patients with OCD. Cognitive-behavioral therapy and SSRIs are considered first-line treatments for OCD.[54]

FIGURE 1. GUIDELINES FOR TREATMENT OF OCD[54]



Note. "Moderate response" means clinically significant but inadequate response.
*Treatment with little supporting evidence (e.g., one or few small trials or case reports or uncontrolled cases series).
CBT=cognitive-behavioral therapy; ERP=exposure and response prevention; MAOI=monoamine oxidase inhibitor; SRI=serotonin reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor

The guidelines recommend an SRI alone for patients who are not able to cooperate with CBT, have previously responded well to a given drug, or prefer treatment with an SRI alone.[54] The guidelines recommend CBT alone, consisting of exposure and response prevention, as initial treatment for patients

who are not too depressed, anxious, or severely ill to cooperate with this treatment modality, or who prefer not to take medications and are willing to do the work that CBT requires.[54] Guidelines note that in some patients, CBT with an SRI is more effective than monotherapy, but is not necessary for all patients; combined treatment should be considered for patients with an unsatisfactory response to monotherapy, for those with co-occurring psychiatric conditions for which SRIs are effective, and for those who wish to limit the duration of SRI treatment.[54] Combined treatment or treatment with an SRI alone may also be considered in patients with severe OCD, since the medication may diminish symptom severity sufficiently to allow the patient to engage in CBT.[54] Uncontrolled follow-up studies suggest that CBT may delay or mitigate relapse when SRI treatment is discontinued.[54]

Pharmacological Treatment of OCD

According to the APA guidelines, U.S. Food and Drug Administration (FDA)-approved medications for OCD, including clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline, are "recommended pharmacological agents."[54] Because the SSRIs have a more favorable side-effect profile than clomipramine, an SSRI is preferred over clomipramine "as a first medication trial."[54] Treatment guidelines note that all SSRIs, including citalopram and escitalopram, which are not FDA-approved for OCD, "appear to be equally effective," and that "individual patients may respond well to one and not to another."[54]

The guidelines state that, in choosing among the SSRIs, the psychiatrist should consider the safety and acceptability of particular side effects for the patient, including any applicable FDA warnings, potential drug interactions, past treatment response, and the presence of co-occurring general medical conditions.[54] For example, paroxetine, the SSRI most associated with weight gain[54, 60] and anticholinergic effect, would not be the first choice for patients with obesity, diabetes mellitus, constipation, or urinary hesitancy.[54] Another factor in choosing among SSRIs is the degree to which they alter metabolism through the hepatic cytochrome P450 enzyme system or uridine 5′-diphosphate glucuronosyltransferases (UGTs), act at the P-glycoprotein transporter, or displace drugs tightly bound to plasma proteins.[54] Many interactions, however, reflect only *in vitro* data, and their clinical importance is not established.[54]

Dosing and Administration of SSRIs. Table 29 displays suggested starting doses, known effective doses, maximum recommended doses, and maximum doses occasionally prescribed for guideline-recommended, first-line treatment for OCD,[54] as well as the dosage range as specified in the product labels. For most patients, the starting dose is that recommended by the manufacturer.[54] Most patients will not experience substantial improvement until 4 to 6 weeks after treatment initiation, and some who will ultimately respond will experience little improvement for as many as 10 to 12 weeks.[54] Medication doses may be titrated weekly in increments recommended by the manufacturer during the first month of treatment. When little or no symptom improvement is seen within 4 weeks of treatment initiation, the dose may be increased weekly or biweekly to the maximum dose comfortably tolerated and indicated.[54] The medication trial is then continued at this dosage for at least 6 weeks.[54]

TABLE 29. DOSING OF GUIDELINE-RECOMMENDED SRIS FOR TREATMENT OF OCD[54]

MEDICATION	STARTING AND INCREMENTAL DOSE (MG/D)[A]	USUAL TARGET DOSE (MG/D)[B]	USUAL MAXIMUM DOSE (MG/D)	OCCASIONALLY PRESCRIBED MAXIMUM DOSE (MG/D)	TARGET DOSAGE RANGE PER LABEL (MG/D)
Clomipramine	25	100-250	250	___[c]	100-250
Citalopram	20	40-60	80	120	Not indicated
Escitalopram	10	20	40	60	Not indicated
Fluoxetine	20	40–60	80	120	20-60 usual; not to exceed 80
Fluvoxamine	100/50	200	300	450	100-300
Paroxetine	20	40–60	60	100	20-60
Sertraline[d]	50	200	200	400	50-200

OCD=obsessive compulsive disorder; SRI=serotonin reuptake inhibitor.
[a] Some patients may need to start at half this dose or less to minimize undesired side effects such as nausea or to accommodate anxiety about taking medications.
[b] These doses are sometimes used for rapid metabolizers or for patients with no or mild side effects and inadequate therapeutic response after 8 weeks or more at the usual maximum dose.
[c] Combined plasma levels of clomipramine plus desmethylclomipramine 12 hours after the dose should be kept below 500 ng/mL to minimize risk of seizures and cardiac conduction delay.
[d] Sertraline is better absorbed with food.

Switching and Augmentation of Treatments for OCD

American Psychiatric Association guidelines note that first treatments rarely produce freedom from all OCD symptoms.[54] When a good response is not achieved after 13 to 20 weeks of weekly outpatient CBT, 3 weeks of daily CBT, or 8 to 12 weeks of SRI treatment (including 4–6 weeks at the highest comfortably tolerated dose), the psychiatrist should decide with the patient when, whether, and how to alter the treatment.[54] This decision will depend on the degree of suffering and disability the patient wishes to accept.[54]

When initial response to pharmacotherapy is unsatisfactory, the psychiatrist should first consider the possible contribution of several factors: interference by co-occurring conditions, inadequate patient adherence to treatment, the presence of psychosocial stressors, the level of family members' accommodation to the obsessive compulsive symptoms, and an inability to tolerate an adequate trial of psychotherapy or the maximum recommended drug doses.[54]

When no interfering factor can be identified, augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial pharmacotherapy.[54] The psychiatrist should first consider augmentation of SSRIs with trials of different antipsychotic medications or with CBT.[54]

Less well-supported treatment strategies include augmenting first-line pharmacotherapy with clomipramine, buspirone, pindolol, riluzole, or once-weekly oral morphine sulfate.[54] However, morphine sulfate should be avoided in patients with contraindications to opiate administration, and appropriate precautions and documentation should occur.[54] If clomipramine is added, appropriate precautions should be utilized with regard to preventing potential cardiac and central nervous system side effects.[54] Less well-supported monotherapies to consider include D-amphetamine, tramadol, monoamine oxidase inhibitors (MAOIs), ondansetron, transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS).[54] Intensive residential treatment or partial hospitalization may be helpful for patients with severe treatment-resistant OCD.[54] Ablative neurosurgery for severe and very treatment-refractory OCD is rarely indicated and, along with deep brain stimulation, should be performed only at sites with expertise in both OCD and these treatment approaches.[54]

DISCONTINUATION OF TREATMENT

Successful medication treatment should be continued for 1 to 2 years before considering a gradual taper by decrements of 10% to 25% every 1 to 2 months while observing for symptom return or exacerbation.[54] In medication discontinuation trials, rates of relapse or trial discontinuation for insufficient

clinical response are substantial but vary widely because of major methodological differences across studies.[54] Thus, discontinuation of pharmacotherapy should be carefully considered, and for most patients, continued treatment of some form is recommended.[54]

TREATMENT OUTCOMES

The gold standard outcome measure in OCD treatment is the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS),[61] a 10-item, clinician-administered measure assessing the severity of OCD obsessions and compulsions (Table 30). The Y-BOCS is the primary outcome measure in all pivotal clinical trials leading to FDA approval for OCD medications.[61] In clinical trials, response to treatment is often assessed by examining the mean change in Y-BOCS score from baseline to endpoint and the proportion of patients achieving a reduction of 25% or more, or 35% or more, on the Y-BOCS.[17]

TABLE 30. YALE-BROWN OBSESSIVE-COMPULSIVE SCALE[61]

ITEM	RANGE OF SEVERITY				
1. Time spent on obsessions	0 hr/d	0–1 hr/d	1–3 hr/d	3–8 hr/d	>8 hr/d
Score	0	1	2	3	4
2. Interference from obsessions	None	Mild	Definite but manageable	Substantial impairment	Incapacitating
Score	0	1	2	3	4
3. Distress from obsessions	None	Mild	Moderate but manageable	Severe	Near constant, disabling
Score	0	1	2	3	4
4. Resistance to obsessions	Always resists	Much resistance	Some resistance	Often yields	Completely yields
Score	0	1	2	3	4
5. Control over obsessions	Complete control	Much control	Some control	Little control	No control
Score	0	1	2	3	4
6. Time spent on compulsions	0 hr/d	0–1 hr/d	1–3 hr/d	3–8 hr/d	>8 hr/d
Score	0	1	2	3	4
7. Interference from compulsions	None	Mild	Definite but manageable	Substantial impairment	Incapacitating
Score	0	1	2	3	4
8. Distress from compulsions	None	Mild	Moderate but manageable	Severe	Near constant, disabling
Score	0	1	2	3	4
9. Resistance to compulsions	Always resists	Much resistance	Some resistance	Often yields	Completely yields
Score	0	1	2	3	4
10. Control over compulsions	Complete control	Much control	Some control	Little control	No control
Score	0	1	2	3	4
Y-BOCS Total Score: 0–7 Subclinical; 8–15 Mild; 16–23 Moderate; 21–31 Severe; 32–40 Extreme					

Other common outcome measures in clinical trials of OCD medications include the Clinical Global Impressions-Severity Scale (CGI-S) and the Clinical Global Impressions-Improvement Scale (CGI-I). The CGI-S requires the clinician to rate on a 7-point scale (1=normal to 7=extremely ill) the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis.[62] The CGI-I requires the clinician to rate (on a 7-point scale [1=very much

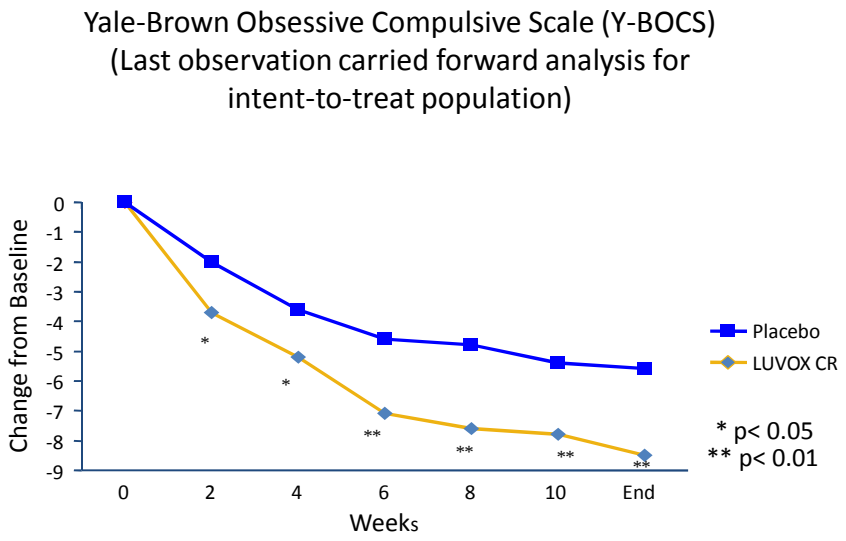
improved to 7=very much worse]) how much the patient's illness has improved or worsened relative to a baseline state.[62]

LUVOX® CR: EXPECTED OUTCOMES OF TREATMENT FOR OCD

EFFICACY

Treatment with LUVOX® CR results in a significant reduction in OCD symptoms at week 12, as indicated by a significant difference between the LUVOX® CR and placebo groups in the change in mean total Y-BOCS score (primary endpoint) from baseline to endpoint (see Figure 2).[63] Over 12 weeks of treatment, patients receiving LUVOX® CR reduced their mean total Y-BOCS scores by 8.5 points (31.7%) compared to a reduction of 5.6 points (21.2%, p=0.001) in the placebo group.[63] Statistical separation from placebo started at week 2 (p<0.05).

FIGURE 2. IMPROVEMENT IN Y-BOCS OUTCOMES: LUVOX® CR VERSUS PLACEBO (N=253)[63]



In addition, significant group differences were seen in the study secondary endpoints. The proportion of responders (Y-BOCS reduction ≥25%) was 63% in the LUVOX® CR group versus 46% in the placebo group (p=0.009).[63] Using a Y-BOCS decrease of 35% or greater to define the response rate, 53 patients (45%) responded in the LUVOX® CR group compared with 36 patients (30%) in the placebo group (p=0.016). Moreover, both the CGI-S and CGI-I scales were significantly reduced in the LUVOX® CR group compared with placebo at 12 weeks.[63] The proportion of patients who were rated as either "very much improved" or "much improved" on the CGI-I was significantly higher in the LUVOX® CR group than in the control group at endpoint (44% versus 23%, p=0.002).[63]

SAFETY

In clinical trials of LUVOX® CR, the most common adverse events with an incidence of ≥5% and at least twice that of placebo were nausea, somnolence, asthenia, diarrhea, anorexia, abnormal ejaculation, tremor, sweating, and anorgasmia. The most frequently seen side effects (e.g., nausea, headache, insomnia, somnolence) were mild and transient in nature.[59] In addition, LUVOX® CR is associated with a weight neutral profile (no significant gain or loss in weight).[1, 63-65] Finally, in patients receiving LUVOX® CR, sexual dysfunction, as measured by the ASEX scale, was not significantly different from placebo at study end and was rarely a reason for premature discontinuation of treatment.[1, 64, 65]

LUVOX® CR was specifically formulated to minimize peak to trough plasma fluvoxamine concentrations compared to fluvoxamine IR. Five crossover studies of over 60 patients evaluated LUVOX® CR formulation prototypes based on rates of dissolution delivery. The slow dissolution delivery prototype successfully fulfilled all of the PK targets and was chosen as the primary formulation for further development.

With the administration of a single dose at night of specifically formulated LUVOX® CR, the patient receives:

- Lower and later peak plasma concentrations (C_{max}) of fluvoxamine compared to fluvoxamine IR, as indicated by C_{max} <85%, with relative time to peak (T_{max}) concentration delayed by >3 hours compared to fluvoxamine IR;[59]
- Similar relative bioavailability (AUC >80%) to fluvoxamine IR;[59] and
- Higher trough concentrations (C_{24h} >110%) than fluvoxamine IR.[59]

The reduced peak to trough plasma level fluctuations with LUVOX® CR may offer the potential for lower incidence of peak-related adverse events.

INTRODUCTION TO SOCIAL ANXIETY DISORDER

CLINICAL FEATURES AND DIAGNOSTIC CRITERIA

Social anxiety disorder, also known as social phobia, emerged as an independent diagnostic entity in DSM-III in 1980,[42] and the diagnostic criteria remained largely the same in the most recent edition of DSM (DSM-IVTR).[2] Prior to 1980, SAD was recognized as a mental disorder but was grouped with all other phobias.[41, 66] The core feature of SAD is marked and persistent fear of one or more social/performance situations in which a person is exposed to unfamiliar people or to possible scrutiny by others.[2] Additional diagnostic criteria are shown in Table 31.

Two subtypes of SAD have been identified: generalized and non-generalized.[2] In generalized SAD, most social situations are feared whereas nongeneralized subtypes fear several types or a single type social or performance situations.[2] Nongeneralized SAD is fairly uncommon, accounting for 17% to 19% of patients with SAD.[38, 67] The vast majority of people with SAD (approximately 83%) fear more than one type of social situation,[67] with generalized SAD accounting for about one-third to one-half of cases.[38, 67]

TABLE 31. DIAGNOSTIC CRITERIA FOR SOCIAL ANXIETY DISORDER

A. A marked and persistent fear of one or more social or performance situations involving exposure to unfamiliar people or possible scrutiny by others. The person fears that he or she will act in a way (or show symptoms of anxiety) that will be humiliating or embarrassing. Note: In children, there must be evidence of the capacity for age-appropriate social relationships with familiar people, and the anxiety must occur in peer settings, not just in interactions with adults.
B. Exposure to the feared situation almost invariably provokes anxiety, which may take the form of a panic attack. Note: In children, the anxiety may be expressed as crying, tantrums, freezing, or shrinking from social situations with unfamiliar people.
C. The person recognizes that the fear is excessive or unreasonable. Note: In children, this may be absent.
D. The feared social or performance situations are avoided or endured with intense anxiety or distress.
E. The condition interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia.
F. In individuals under age 18, the duration is at least 6 months.
G. The fear or avoidance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition and is not better accounted for by another mental disorder (e.g., Panic Disorder With or Without Agoraphobia, Separation Anxiety Disorder, Body Dysmorphic Disorder, A Pervasive Developmental Disorder, or Schizotypal Personality Disorder).
H. If a general medical condition or another mental disorder is present, the fear in criterion A is unrelated to it (e.g., the fear is not of stuttering, trembling in Parkinson's disease, or exhibiting abnormal eating behavior in Anorexia Nervosa or Bulimia Nervosa).

Specify if:
Generalized: if the fears include most social situations (also consider the additional diagnosis of Avoidant Personality Disorder).

Common fearful situations in persons with SAD are shown in Table 32.[68] Persons with SAD often display hypersensitivity to criticism, negative evaluation, or rejection; difficulty being assertive; and low self-esteem or feelings of inferiority.[2] They may manifest poor social skills or observable signs of anxiety.[2]

TABLE 32. COMMON FEARFUL SITUATIONS IN SAD[68]

- Asking questions in groups
- Attending social gatherings
- Being assertive
- Being introduced to others
- Indirect evaluation (e.g., taking a test)
- Interacting with "important" people
- Being watched doing something (e.g., eating, writing)
- Making "small talk"
- Meeting or talking with strangers
- Public speaking or performing
- Small group discussion
- Using public restrooms
- Using the telephone

EPIDEMIOLOGY OF SAD

Social anxiety disorder is the 4th most common psychiatric disorder, with an estimated lifetime and 1-year prevalence of approximately 12%[3] and 6.8%[69], respectively. Studies suggest that SAD is more common in women than men.[2] Half of all persons with SAD have onset by 13 years and 90% by age 23 years.[32]

PATHOGENESIS

Evidence suggests that both heredity and environment contribute to the development of SAD. Toddlers who appear to be shy and have inhibited temperament are at increased risk for the development of SAD by the time they reach their teens, although the disorder does not develop in most shy children.[70] Overprotective parenting has been associated with SAD, although the extent to which such parenting is a contributing cause, as compared with a response to a child with SAD, is unclear.[71] Neuroimaging studies in affected persons have shown increased reactivity in the amygdala to social cues, such as faces.[72] Other studies have shown abnormalities in serotonin and dopamine systems.[73]

Twin and family studies suggest that there is a genetic component of SAD. In a twin study, the concordance of SAD was 10% greater in identical compared with non-identical twins.[74] Family studies have noted a significantly elevated risk for SAD in relatives of probands with SAD.[75] One study found a 16% rate of SAD among relatives of persons with SAD compared with a 5% rate in controls.[75] Another study found a similar increased risk of generalized SAD in family members of probands with this subtype.[76] A third study found a 10-fold higher risk of SAD among first-degree relatives of probands with SAD than among comparison probands.[77]

COMORBIDITY

As with other psychiatric conditions, the majority of patients (69%) diagnosed with SAD had at least one additional lifetime comorbid psychiatric disorder.[33] SAD without comorbidity is referred to as "uncomplicated SAD"[33] or "pure SAD"[67] while SAD with comorbid psychiatric disorders is called "comorbid SAD."[33] The comorbidities with the highest association with SAD include agoraphobia, simple phobia, somatization disorder, and major depression (Table 33).[33] For individuals with comorbid disorders (other than agoraphobia, simple phobia and schizophrenia), SAD preceded the comorbid disorder in 76.8% of cases.[33]

TABLE 33. LIFETIME RATES PER 100 OF OTHER PSYCHIATRIC DISORDERS IN SAD

	No. (%)		Logistic Regression	
Comorbidity	SAD (N=361)	No SAD (N=13,176)	Adjusted Odds Ratio*	95% Confidence Interval
Panic Disorder	17 (4.7)	177 (1.3)	3.24	1.94–5.41†
OCD	40 (11.1)	326 (2.5)	4.36	3.07–6.21†
Major Depression	60 (16.6)	530 (4.0)	4.41	3.27–5.95†
Bipolar Disorder	17 (4.7)	139 (1.1)	4.09	2.43–6.90†
Dysthymia	45 (12.5)	405 (3.1)	4.30	3.07–6.02†
Alcohol Abuse	68 (18.8)	1,608 (12.2)	2.20	1.64–2.96†
Drug Abuse	47 (13.0)	655 (5.0)	2.85	2.04–4.00†
Somatization Disorder	7 (1.9)	29 (0.2)	8.02	3.44–18.67†
Agoraphobia	162 (44.9)	807 (6.1)	11.81	9.42–14.82†
Simple Phobia	213 (59.0)	1,743 (13.2)	9.17	7.33–11.49†

OCD=obsessive compulsive disorder; SAD=social anxiety disorder.
Adjusted for age, sex, and site.
† p<0.001.

COURSE OF ILLNESS

The disorder usually begins in the mid-teens, sometimes emerging out of a childhood history of social inhibition or shyness.[2] Some individuals report an onset in early childhood.[2] Onset may abruptly follow a stressful or humiliating experience, or it may be insidious.[2] The course of SAD is often continuous with a lifelong duration, although the disorder may attenuate in severity or remit during adulthood.[2] Severity of impairment may fluctuate with life stressors and demands.[2] For example, SAD may diminish after a person with fear of dating marries and may reemerge after the death of a spouse.[2] A job promotion to a position requiring public speaking may result in the emergence of SAD in someone who previously never needed to speak in public.[2]

DIFFERENTIAL DIAGNOSIS

Table 34 shows the psychiatric diagnoses that have some degree of overlap with SAD and features that may distinguish these disorders from SAD. In persons with panic disorder, panic attacks are not limited to social situations, and the diagnosis of SAD is not made when the only social fear is of being seen while having a panic attack.[2] In SAD, the situations that are avoided are limited to those involving possible scrutiny by other people whereas, in panic disorder with agoraphobia and agoraphobia without history of panic disorder, fears involve clusters of situations that may or may not involve scrutiny by others.[2] As well, in agoraphobic disorders, people prefer to be with a trusted companion while in SAD may be less anxious without a companion present.[2] Children with separation anxiety disorder may avoid social situations due to separation concerns but are usually comfortable in social situations in their own home, whereas those with SAD are anxious in all types of social settings. Although people with generalized anxiety disorder or specific phobia may be fearful of humiliation or embarrassment, this is not the main focus of their fear or anxiety.[2] Children with generalized anxiety disorder may worry about their performance, but this anxiety occurs whether or not they are being evaluated by others.[2] In pervasive developmental disorder and schizoid personality disorder, social situations are avoided due to lack of interest in relating to others whereas those with SAD have a capacity for and interest in social relationships.[2] To qualify for SAD, children must have at least one age-appropriate social relationship with someone outside of the immediate family.[2] Avoidant personality disorder shares many features with SAD and may be an alternate conceptualization of the same or similar condition.[2]

TABLE 34. DIFFERENTIAL DIAGNOSIS OF SAD

DIFFERENTIAL DIAGNOSIS	DISTINGUISHING FEATURES FROM SAD
Panic disorder with or without agoraphobia	Panic attacks are not limited to social situations. Diagnosis of SAD is not made when only social fear is fear of having a panic attack.
Agoraphobia with or without panic disorder	Agoraphobics fear a variety of situations, not just those involving scrutiny by others. Agoraphobics are calmed by the presence of a trusted companion, while social phobics find the presence of a companion anxiety provoking.
Separation anxiety disorder	Children with separation anxiety disorder are comfortable in social situations in their own homes, whereas those with SAD are uncomfortable in all social situations.
Generalized anxiety disorder	Persons with GAD do not have fears that strictly center on humiliation or embarrassment. Worry or fear in persons with GAD is not focused on fear of scrutiny by others.
Pervasive developmental disorder	Social situations are avoided due to lack of interest rather than anxiety.
Schizoid personality disorder	Social situations are avoided due to lack of interest rather than anxiety.
Avoidant personality disorder	Shares many features with SAD; may be an alternate conceptualization of SAD.

GAD=generalized anxiety disorder; SAD=social anxiety disorder.

Adapted from the American Psychiatric Association. (DSM-IV-TR) Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text revision. Washington, D.C.: American Psychiatric Association; 2000.

IMPACT OF SAD ON FUNCTIONING AND QUALITY OF LIFE

Social anxiety disorder is a chronic, debilitating psychiatric disorder associated with educational underachievement, increased financial dependency, decreased work productivity, social impairment, and reduced quality of life.[33, 39, 67] Overall, individuals with SAD have similar levels of lifetime disability as those with major depression.[35]

Children and adolescents with SAD are twice as likely to have poor grades, and they are 2 to 4 times as likely to evidence conduct disorder behavior (e.g., runaway behavior, fighting, telling lies, and stealing), as those without SAD.[39] SAD increases the likelihood of underachievement in school because of anxiety due to testing, class participation, and public speaking.[2] In the ECA study, one half of those with social phobia were unable to complete high school.[33]

Approximately 85% of patients with the disorder experience occupational difficulties caused by their inability to meet the social demands of securing and maintaining employment or relationships.[68] Poor occupational functioning results in more frequent unemployment, lower income levels, and greater

reliance on public aid. Persons with SAD are 3 times more likely to repeatedly be terminated from employment and 4 times more likely to be frequently absent or late to work, compared with those without SAD.[39] In a case-control study among primary care patients, those with SAD were 3 times more likely to be unemployed and reported significantly greater impairment in quality of life and work performance, than age- and sex-matched controls with a chronic physical illness.[67] A diagnosis of SAD is associated with a 19% reduction in wages compared with no diagnosis ($p<0.001$).[35] In the ECA study, 70% of persons with SAD were in the lowest two quartiles of socioeconomic status, and approximately 22% were on welfare, a rate twice that of persons without psychiatric disorders (OR 1.89, $p<0.01$).[33]

Compared to persons with a chronic physical disorder, those with SAD were more likely to report severe impairments in functioning, particularly in the areas of interpersonal relationships and education/career.[34] Patients with SAD report significantly greater impairment in family and romantic relationships and social networks than patients with no psychiatric diagnosis.[78] They often have decreased social support networks and are less likely to marry.[2, 79] In more severe cases, individuals may have no friends or cling to unfulfilling relationships, completely refrain from dating, or remain with their family of origin.[2]

The severe disability and poor quality of life associated with the disorder increases the risk of suicidality among persons with SAD. One of every five pure SAD patients has made a suicide attempt, a rate 4 times ($p<0.001$) that seen among nonpsychiatric patients.[35] Patients with comorbid SAD are almost 6 times more likely to have made a suicide attempt than normal controls.[33]

SAD IS UNDER-DETECTED AND UNDER-TREATED

Even though SAD begins early in life and causes significant impairment in functioning, many afflicted persons, particularly those without comorbid psychiatric conditions, are not recognized as having a mental disorder and do not receive adequate treatment. In the ECA study, two thirds (72%) of respondents with SAD reported that they had never received outpatient mental health treatment.[33] Data from the NCS revealed that only 15% of patients with SAD report having sought help from a physician or mental health professional during the past year.[80] In another study, only 1 in 5 persons with SAD reported having sought help for emotional problems.[67]

Reasons for the under-detection and under-treatment of SAD are shown in Table 35. Patients may avoid disclosing their symptoms due to embarrassment or shame, and physicians may focus on treating the symptoms that patients are more willing to disclose, such as somatic complaints and depression.[68] In the ECA study, only 5.4% of persons with pure SAD sought help from a mental health professional, whereas 17% sought medical treatment for their symptoms.[33] In a study of patients presenting to outpatient psychiatric services, only one half of patients with primary SAD reported that they were seeking help for their SAD symptoms, whereas half reported that they were seeking help for other psychiatric symptoms.[81]

Primary care physicians have low levels of accuracy in identifying these patients with SAD. A 3-item version of the longer Social Phobia Inventory (SPIN), called the Mini-SPIN, has demonstrated good sensitivity and specificity in identifying managed care patients with SAD.[82] Less than half of primary care patients with SAD report having seen a mental health professional,[83] and only 1 in 4 patients diagnosed with SAD via a structured interview were correctly identified by their primary care doctor as having the disorder.[36] In a study comparing help-seeking among persons with panic disorder, generalized anxiety disorder, and SAD, those with SAD had the longest delay between onset of symptoms and consultation with a family physician (mean 46 months), were most likely (73%) not to receive a psychiatric diagnosis by their family physician, and were least likely (9%) to be correctly diagnosed by their family doctor.[37] In addition, patients with SAD were no more likely to be recognized by their doctor as having psychological problems than controls.[36]

Patients with SAD are under-treated. In one study, only 16% of patients with SAD treated in a primary care setting were taking some type of psychotropic medication.[38] Because this small group of treated patients also had comorbid depression, it seems likely that patients were receiving medication targeting that disorder rather than SAD.[38] In a recent study in which primary care patients were surveyed about

the care received over the past 3 months, only 34% of those with SAD reported having received appropriate treatment for their disorder (either an appropriate anxiolytic for at least 6 weeks or CBT).[84] Finally, in a retrospective review of HMO records, less than one half of those meeting criteria for SAD had been treated.[35]

Other barriers to SAD patients being correctly diagnosed and treated include physician low awareness of SAD and lack of knowledge of effective treatments,[85] and patient beliefs about the nature of SAD.[86] Regarding the latter, the very early onset of this disorder, with high overlap with trait-like features such as shyness and avoidance, frequently leads patients and physicians to conclude that SAD is simply a stable personality feature that is not amenable to change.[86] Patients' belief that they have "always been this way" contributes to a lack of help-seeking behavior, with many patients not seeking help until many years after disease onset.[86]

TABLE 35. OBSTACLES TO EFFECTIVE TREATMENT OF SAD[68]

- Patient avoids treatment because of fear, shame, or stigma.
- Screening devices for assessing SAD are unavailable.
- Assessment and treatment are misdirected toward specific symptoms (e.g., somatic complaints) or comorbid conditions (e.g., depression, substance use problems) rather than toward the social phobia syndrome.
- Affordable and expert care is unavailable.
- Physician or patient lacks knowledge about effective treatment options.
- Patient or physician trivializes phobia or views it as characterologic and unchangeable (e.g., patient is "just shy").

Burden of SAD to the Healthcare System

People with untreated anxiety disorders make up a large proportion of the people who overuse primary care for only vaguely defined physical complaints.[87, 88] A recent anxiety disorders cost-of-illness study estimated that unnecessary medical care costs represented the largest single component of the cost of anxiety disorders in the U.S., equal to $23 billion (non-psychiatric medical costs) per year out of a total $42.3 billion spent.[89] This suggests that inappropriate treatment of undiagnosed and misdiagnosed patients appears to contribute meaningfully to the overall economic burden.

In a study of 511 adults presenting for routine medical care, those with SAD made more than 2 times as many visits to their medical providers in the previous 6 months (7.58, SD=7.91) than did primary care patients without mental illness (3.42; SD=2.96; U=1141; p<0.0006).[38] Persons with SAD also made significantly more visits in the previous 6 months to mental health providers (psychiatrists, psychologists, social workers, psychiatric nurses, or counselors) than did primary care patients without mental illness, though few such visits were made by either group (3.08 versus 0.32, respectively, p<0.0003).[38]

Other studies have confirmed that persons with SAD tend to over-utilize outpatient medical care. In the North Carolina ECA study, persons with SAD rated their general health as fair or poor more often than controls (33.4% versus 18.3%), and reported more frequent medical outpatient visits in the previous 6 months (6.2 versus 0.8, p=0.0001), which was unexplained by comorbidity.[39] In the 5-site ECA study, SAD was associated with significantly elevated rates of seeking outpatient treatment for emotional problems (OR 1.49, p<0.01) and psychiatric outpatient treatment (OR 1.43, p<0.05), but was not associated with increased utilization of inpatient psychiatric treatment or emergency department services.[33] Among persons with pure SAD, there was an elevated rate of outpatient medical treatment (OR 1.85, p<0.05), but no increased rates of outpatient treatment overall, psychiatric hospitalization, or emergency department use.

To date, there have been no population-based cost-of-illness studies of SAD in the U.S. However, in 2001, Katzelnick and colleagues estimated the direct costs (in 1998 dollars) associated with SAD in a

managed care population.[35] Patients with SAD over-utilized outpatient care, resulting in higher direct costs: persons with pure and comorbid SAD had an annual mean direct cost of $2,536 (p=0.09) and $2,784 (p=0.05), respectively, compared to $1,887 for persons without psychiatric disorders.[35]

PLACE OF LUVOX® CR IN THE TREATMENT OF SAD

INDICATIONS FOR TREATMENT

Because anxiety disorders, such as SAD, are chronic in nature and have a high level of associated disability, most patients who meet diagnostic criteria are likely to benefit from some form of treatment.[90] The need for treatment is determined by the severity and persistence of symptoms, the presence of comorbid mental disorder or physical illness, the level of disability and impact on social functioning, concomitant medication, and a history of good response to, or poor tolerability of, previous treatment approaches.[90] An expert panel has recommended that treatment of SAD be considered for all patients who meet diagnostic criteria for SAD.[91]

GOALS FOR TREATMENT

The primary goal of treatment is to reduce social anxiety to manageable levels, but even modest reductions in avoidance and discomfort may be highly valued by affected persons.[92]

TREATMENT OPTIONS FOR SAD

Currently, there are no published clinical guidelines for the treatment of SAD in the U.S. Treatment options include CBT, pharmacotherapy, and CBT combined with pharmacotherapy. Cognitive-behavioral therapy and pharmacotherapy appear to have similar efficacy for the treatment of SAD,[93-97] and the combination of treatments does not appear to be more efficacious than either treatment alone.[93] Treatment planning should be done after the benefits and risks of treatment options have been discussed with the patient.[68] Considerations in treatment planning should include the patient's preference, the severity of presenting symptoms, the degree of functional impairment, psychiatric and substance-related comorbidity, and long-term treatment goals.[68] Time-limited use of low-dose benzodiazepine therapy may help with initial symptom relief until slower-acting pharmacotherapy or CBT takes effect.[68] For circumscribed SAD, data suggest that CBT with or without initial as-needed use of beta-blockers may be effective.[68]

Pharmacotherapy for SAD

Currently, the FDA has approved paroxetine (IR and CR), sertraline, venlafaxine XR, and LUVOX® CR for the treatment of SAD. The efficacy and safety of these medications in the treatment of SAD have been established in more than 20 randomized, controlled trials.[92] Response rates range from 50% to 80% after 8 to 12 weeks of treatment.[92] Head-to-head trials comparing SSRIs with one another or with a serotonin and norepinephrine reuptake inhibitor (SNRI) have not demonstrated that any one medication is superior to the others in the treatment of SAD,[92] and it is likely that SSRIs have similar efficacy in the treatment of SAD.[98]

Treatment with an SSRI or an SNRI is commonly initiated at half the usual effective dose, and the dose is increased after 1 week (Table 36).[1, 99, 100] The dose-response curve for these agents is relatively flat in SAD,[101] but because some patients may benefit from higher doses, clinicians commonly increase the dose as tolerated in those who have no response after 4 weeks of the therapy.[92] Although many patients report improvement during the first few weeks of treatment, more than a quarter of those who do not have a response at week 8 may have a response during an additional 4 weeks of treatment at the same dose, suggesting that an initial trial should last 12 weeks.[92] Patients who have a response during those 12 weeks should receive maintenance treatment to minimize the risk of relapse.[92] The usefulness of these medications during longer periods of treatment is limited in some cases by adverse effects, including sexual dysfunction and weight gain.[92]

Benzodiazepines. Although evidence of the efficacy of benzodiazepines in SAD is more limited than that for SSRIs and SNRIs, benzodiazepines are commonly used in the treatment of patients who cannot tolerate or do not have an adequate response to SSRIs or venlafaxine.[92] The relatively long-acting benzodiazepine clonazepam, given daily in divided doses, appeared to be highly effective in generalized

SAD in a controlled trial (response rate, 80%) and in several open trials.[102] A single controlled trial of alprazolam was inconclusive.[96] In most patients, tolerance rapidly develops to the sedative effects of benzodiazepines, but not to the anxiolytic effects.[92] Long-term use (more than 2 weeks) may result in physical dependence, and abrupt discontinuation of the medication should be avoided because of the risk of rebound anxiety and withdrawal symptoms (including tremor, insomnia, and in rare cases, seizures).[92] A gradual tapering of the dose of clonazepam (a decrease of 0.25 mg every 2 weeks), however, has been shown to be well tolerated by patients with SAD.[103] Benzodiazepines are not recommended as monotherapy for patients who have major depression in addition to SAD and should be avoided in patients with a history of substance abuse.[92]

Other Medications. Gabapentin and pregabalin are structurally related anticonvulsants that have been reported to be significantly superior to placebo in reducing symptoms of generalized SAD in single controlled trials, although response rates for each were less than 45%.[104, 105] In a recent small, placebo-controlled trial, mirtazapine, an antidepressant with a mechanism of action different from that of other available antidepressants, was shown to be effective at a fixed dose of 30 mg per day in women with SAD.[106] The monoamine oxidase inhibitor (MAOI) phenelzine has been shown to be effective in SAD in randomized clinical trials,[96, 107] but presents safety concerns and requires that patients follow a low-tyramine diet to prevent hypertensive crisis, and therefore is not regarded as a first-line treatment.[92] Moclobemide, a reversible inhibitor of monoamine oxidase A, appears to be safer than standard MAOIs, although meta-analyses have found it less effective in SAD than the SSRIs;[107] it is not available in the U.S. For non-generalized SAD, several studies suggest that beta-blockers such as propranolol, taken as needed about an hour before a performance, may be helpful in performance-type SAD.[108]

TABLE 36. DRUGS WITH ESTABLISHED EFFICACY FOR SAD[92]

DRUG	STARTING DOSE (MG/DAY)	TARGET DOSE (MG/DAY)	LABEL DOSE RANGE (MG/DAY)	SIDE EFFECTS
SSRIs				
Paroxetine IR* and CR*	10; 12.5	10-60; 12.5-75	20-60; 12.5-75	Sexual dysfunction, headache, nausea, sedation, insomnia, sweating, withdrawal syndrome
Sertraline*	50	50-200	50-200	
Fluvoxamine IR and CR*	50; 100	50-300; 100-300	Not indicated;100-300	
Escitalopram	5	5-20	Not Indicated	
SNRI				
Venlafaxine XR*	75	75–375	75-225	Same as SSRIs; also hypertension
MAOI				
Phenelzine	15	30-90	Not Indicated	Sedation, insomnia, hypotension, weight gain, low-tyramine diet required to prevent hypertensive reaction
Other Antidepressants				
Mirtazapine	15-30	30-60	Not Indicated	Dry mouth, weight gain, sedation
Benzodiazepines				
Clonazepam	0.25	0.50-4.0	Not Indicated	Sedation, ataxia, cognitive impairment, withdrawal syndrome
Alprazolam	0.25	0.25-1.0	Not Indicated	
Lorazepam	0.50	0.50-2.0	Not Indicated	
Beta-blockers				
Propanolol	10	10-40	Not Indicated	Hypotension, bradycardia

*FDA approved for SAD
FDA=food and drug administration; MAOI=monoamine oxidase inhibitor; SAD=social anxiety disorder; SNRI =serotonin and norepinephrine reuptake inhibitor; SSRI =selective serotonin reuptake inhibitor.

DURATION OF TREATMENT

There are no established guidelines for the duration of treatment for SAD, and little is known about long-term management of the disorder. Many patients with SAD may require long-term therapy. Within 6 months of discontinuing pharmacotherapy, up to 40% of patients will relapse.[109, 110] In one study, 88% of responders who completed 2 years of pharmacotherapy deteriorated after discontinuing therapy for at least 1 month.[111] In a study examining the durability of response with phenelzine versus CBT in patients who had responded to a 12-week, acute-phase treatment, treatment gains were maintained during 6

months of maintenance therapy in both groups; however, during a subsequent 6 months of follow-up without any treatment, 30% of patients treated with phenelzine relapsed, compared with 0% of CBT patients (p=0.09).[112] In an 11-week open-label trial of paroxetine followed by a 12-week, double-blind, placebo-controlled trial, relapse rates were 13% for the group that continued paroxetine therapy versus 63% in the group that was switched to placebo.[113] Thus, it appears that a high proportion of patients tend to relapse when medication is discontinued. At present, there is no way to predict which patients will do well when medication is discontinued or which patients will require long-term treatment.[54]

Long-term pharmacotherapy for SAD results in continued improvement and decreased relapse rates. LUVOX® CR,[114] paroxetine,[109, 113, 115] sertraline,[110] escitalopram,[116] and venlafaxine XR[101] have been associated with continued improvements over 5 to 6 months. Open follow-up of patients treated with moclobemide showed that benefits were maintained with ongoing therapy, and discontinuation of medication, even after 2 years of therapy, was associated with deterioration in most patients.[111, 117] Paroxetine,[109, 113] sertraline,[110] and escitalopram[118] have demonstrated significant reductions in relapse rates over 6 months in placebo-controlled discontinuation trials. Relapse rates were 4% to 14% with ongoing SSRI treatment, compared with 36% to 39% for placebo.[109, 110] These data suggest that, if a patient responds acutely to a medication, its continued use likely will effectively prevent relapse.

LUVOX® CR: EXPECTED OUTCOMES OF TREATMENT FOR SAD

The Liebowitz Social Anxiety Scale (LSAS) is used extensively in clinical trials and is accepted as the gold standard for clinician rating of clinical severity in SAD.[91] The LSAS rates 24 potentially anxiety-producing situations for severity of fear and anxiety and frequency of avoidance.[119] An LSAS score of 80 to 120 indicates severe illness, 60 to 80 indicates moderate illness, and 40 to 60 indicates mild illness.[120] A proposed cutoff score for symptomatic remission is 30 or less, as supported by data suggesting that scores of healthy people and those with SAD separated with good sensitivity and specificity at 30.[121]

In a randomized, double-blind clinical trial involving 279 patients with SAD, LUVOX® CR resulted in a significant reduction in the LSAS (primary endpoint) compared with placebo at 12 weeks with statistical separation beginning at week 4.[64] The mean change from baseline on the LSAS was -26.7 (29.6% decrease) for the LUVOX® CR group and -12.9 (14.5% decrease) for the placebo group ($p<0.01$).[64] For the LUVOX® CR group, this represents a reduction from a mean of 90 (indicating severe illness) to a mean of about 63 (indicating mild to moderate illness).[64] In addition, LUVOX® CR was also statistically superior to placebo on all secondary efficacy measures, including the Sheehan Disability Scale, CGI-S, CGI-I, and the Patient Global Impression (PGI) scale.[64] The response rate based on the CGI-I scale, defined as a score of "very much improved" or "much improved" at endpoint, was 33.9% for the LUVOX® CR group and 16.7% for the placebo group ($p<0.001$).[64]

In another 12-week, randomized, double-blind, placebo-controlled clinical trial involving 300 patients with SAD, LUVOX® CR resulted at week 12 in a 36.1 point reduction (37%) from baseline on the primary endpoint (LSAS) compared with a 27.3 point (28%) reduction in placebo group ($p=0.02$).[65] Again, statistical separation from the placebo group occurred at week 4, although it was not sustained at week 6 in this study.[65] Significant group differences in favor of LUVOX® CR also were seen in the secondary endpoints CGI-I, CGI-S, and the Sheehan Disability Scale, but not the PGI.[65]

ADVERSE EVENTS ASSOCIATED WITH SAD TREATMENTS

SSRIs have a more favorable safety profile than benzodiazepines and MAOIs.[98] Adverse events frequently associated with SSRIs are gastrointestinal symptoms (e.g., nausea, constipation); central nervous system effects such as headache, somnolence, and insomnia; and sexual dysfunction (delayed ejaculation in men, delayed orgasm or anorgasmia in women, decreased libido in both men and women).[98] The SNRI venlafaxine has a side effect profile similar to that of the SSRIs and also may cause hypertension.[92] Benzodiazepines are associated with sedation during initial usage, although patients become tolerant to this side effect within a few days.[98] A less frequent side effect of benzodiazepines is ataxia, which is particularly problematic in the elderly, who are at elevated risk of an overdose due to age-related reduced metabolic rate and for whom falling is particularly dangerous.[98] Persons with SAD who take benzodiazepines on a regular basis are at risk for becoming physically dependent on these drugs.[98] Although MAOIs are effective in the treatment of SAD, patients may develop a potentially fatal hypertensive reaction if they fail to follow a tyramine-restricted diet.[68] Common adverse effects at therapeutic dosages include postural hypotension, sedation, and sexual dysfunction and weight gain.[68] Some common over-the-counter medications, such as cold and cough remedies, are contraindicated in patients using MAOIs.[68] Reversible MAOIs, such as moclobemide, do not require dietary restrictions, but they are not yet available in the U.S.[68]

Perhaps the most substantial pharmacokinetic difference among SSRIs is in their potential for drug-drug interactions via the inhibition of cytochrome P450 (CYP) isoenzymes. Whereas fluoxetine and paroxetine are potent inhibitors of CYP2D6, other SSRIs have not evidenced significant inhibitory effects of this isoenzyme.[122] Fluvoxamine is a potent inhibitor of CYP1A2, CYP2C19, and CYP3A4 and fluoxetine is a moderate inhibitor of CYP2C19.[122] In contrast, citalopram, escitalopram, and sertraline have few significant drug-drug interactions.[54] Despite evidence of potent *in vitro* drug-drug interactions for some SSRIs, such interactions are rarely clinically important due to innate physiological mechanisms that compensate for enzyme interactions.[122]

PATIENT MONITORING

The effectiveness of pharmacotherapy for the long-term treatment of SAD has not been systematically evaluated in adequate and well-controlled trials.[1, 99, 100, 123, 124] Therefore, the health care provider who elects to prescribe therapies for extended periods should regularly re-evaluate the long-term usefulness of the drugs for the individual patients.[1, 99, 100, 123, 124]

CLINICAL EVIDENCE FOR LUVOX® CR IN OCD

Hollander E, Koran LM, Goodman WK, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. J Clin Psychiatry 2003;64(6):640-7.

Objectives: This phase 3 study aimed to investigate the efficacy and safety of once-daily dosing of fluvoxamine CR in adult patients with OCD.

Subjects and Methods: This was a multicenter, randomized, double-blind, parallel-arm, placebo-controlled study comparing the efficacy and safety of flexible dosing of fluvoxamine CR (100 to 300 mg/d) with placebo over a 12-week period in adult patients with OCD. Eligible patients were male and female outpatients, age 18 years or older who met DSM-IV criteria for OCD (diagnosis confirmed through the Structured Clinical Interview for DSM-IV), had a score of ≥21 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), and had a score of 16 or lower on the 17-item Hamilton Rating Scale for Depression (HAM-D). Subjects were excluded if they had a primary DSM-IV diagnosis other than OCD; were at significant risk for suicide; had unstable or serious medical conditions, clinically significant ECG abnormalities, or clinically significant laboratory abnormalities; had a positive urine drug test at screening; were women who were pregnant, lactating, or of childbearing potential and not using adequate contraception; had received electroconvulsive therapy within 90 days of the study start or during the study; had a documented history of non-response to an adequate trial of an SRI for the treatment of OCD, defined as no clinically meaningful improvement after at least 6 weeks of therapy with a therapeutic dose; or were taking concomitant psychotropic or psychotherapeutic drugs, astemizole, cisapride, terfenadine, theophylline, warfarin, digoxin, diltiazem, propanolol, or over-the-counter herbal remedies or weight loss agents with suspected psychotropic properties during the study.

A total of 253 patients were enrolled and randomized to treatment (127 LUVOX® CR and 126 placebo). There were no statistically significant differences in the baseline characteristics of the two groups (Table 37).

TABLE 37. CHARACTERISTICS OF OCD PATIENTS AT BASELINE

CHARACTERISTIC	LUVOX® CR (N=127)	PLACEBO (N=126)	P VALUE
Age, y			
Mean ± SE	38.1 ± 1.1	36.7 ± 1.0	0.335
Range	19–70	18–69	
Gender, n (%)			0.232
Male	51 (40)	41 (53)	
Female	76 (60)	85 (67)	
Duration of current OCD episode, y			
Mean ± SE	16.2 ± 1.2	16.5 ± 1.2	0.959
Range	0–55	0–55	
Baseline Y-BOCS score			
Mean ± SE	26.6 ± 0.3	26.3 ± 0.3	0.460
Range	21–38	21–36	
Baseline CGI-S score			
Mean ± SE	4.7 ± 0.1	4.6 ± 0.1	0.157
Range	4–7	3–7	
HAM-D score			
Mean ± SE	6.8 ± 3.6	7.3 ± 3.7	0.190

CGI-S=Clinical Global Impressions-Severity of Illness Scale; HAM-D=Hamilton Rating Scale of Depression; OCD=Obsessive Compulsive Disorder; SE=Standard Error; Y-BOCS=Yale-Brown Obsessive Compulsive Scale.

Subjects randomized to receive LUVOX® CR began at a bedtime dose of 100 mg and were titrated weekly as tolerated in 50 mg increments to a bedtime dose of between 100 and 300 mg/d over the first 6 weeks of treatment; thereafter, the dose was to remain constant for the duration of the double-blind period. Subjects unable to tolerate the 100 mg dose during the first week of treatment were discontinued

from the study. After week 1 and through the end of week 6, the dose could be decreased to 1 capsule (from the usual dose of 2 capsules) in the event of an intolerable adverse event (AE). If an intolerable AE requiring a dose decrease occurred after week 6, the subject was discontinued from the study. No increase in dose was permitted after a decrease. Adherence to study regimen was assessed by pill count, and patients who took less than 80% or more than 120% of a prescribed dosage during the interval between visits on 2 or more occasions were discontinued from the study.

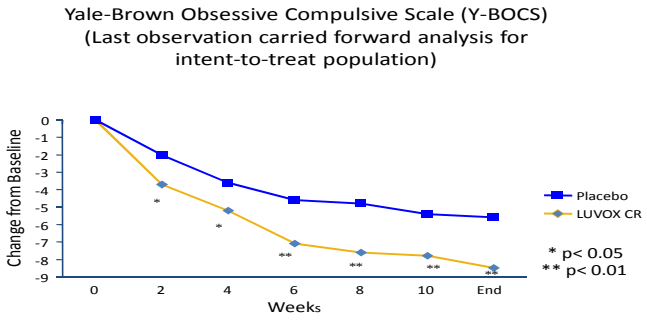
Efficacy was assessed using the Y-BOCS (primary endpoint) and CGI-S scales at screening, baseline (day 1), and at the end of weeks 2, 4, 6, 8, 10, and 12. The CGI-I scale was administered at every visit after baseline. Safety measures assessed at each visit included vital signs, weight, AEs, and concomitant medications. An ECG and physical examination were performed at screening and week 12 visits. Laboratory testing was performed at the screening, baseline and at weeks 6 and 12.

Efficacy Results: All analyses of efficacy parameters were performed on the intent-to-treat population, which included all randomized patients who took at least 1 dose of study medication, had a baseline efficacy evaluation, and had at least 1 evaluable post-baseline efficacy measurement. Statistical analyses were performed using data from visitwise and last observation carried forward (LOCF) algorithms.

Of the 253 randomly assigned patients, 117 (92%) in the LUVOX® CR and 120 (95%) in the placebo group were included in the efficacy analyses. The mean daily dose of LUVOX® CR was 210 mg during the study and 271 mg at endpoint, compared with placebo doses of 231 mg and 293 mg, respectively. Most patients receiving LUVOX® CR (86%) and placebo (92%) were adherent (took 80% to 120% of prescribed doses).

Subjects treated with LUVOX® CR experienced a statistically significant improvement from week 2 compared with those treated with placebo in the primary endpoint of Y-BOCS total score (Figure 3). The mean ± standard error decrease from baseline to endpoint in the Y-BOCS total score was 8.5 ± 0.7 (31.7% change) in the LUVOX® CR group versus 5.6 ± 0.7 (21.2% change) in the placebo group (p=0.001) (Table 38).

FIGURE 3. IMPROVEMENT IN Y-BOCS OUTCOMES: LUVOX® CR VERSUS PLACEBO (N=253)[63]



Data on file, NDA 22-033

Defining a response by Y-BOCS decrease of ≥25%, 63% of patients receiving LUVOX® CR responded versus 46% of patients receiving placebo (p=0.009). Defining a response by Y-BOCS decrease of ≥35%, 45% of patients receiving LUVOX® CR responded versus 30% of patients receiving placebo (p=0.016). When remission was defined as a Y-BOCS total score of ≤16 at endpoint, 44% of LUVOX® CR and 31% of placebo patients experienced remission (p=0.045). When remission was defined as a Y-BOCS total score of ≤8 at endpoint, 18% of LUVOX® CR and 8% of placebo patients experienced remission (p=0.019).

Analysis of both Y-BOCS obsession and compulsion subtotals also revealed a significant treatment difference in favor of LUVOX® CR at endpoint, with mean reductions on the obsession subtotal of 39.6% versus 24.4% in the placebo group (p<0.001) and compulsion subtotal of 34.3% versus 24.8% in the placebo group (p=0.048).

TABLE 38. EFFICACY PARAMETERS IN OCD SUBJECTS

EFFICACY PARAMETER	LUVOX® CR (N=117)	PLACEBO (N=120)	P-VALUE
Y-BOCS total score			
Baseline	26.8 ± 0.3	26.4 ± 0.3	
Endpoint	17.6 ± 1.1	21.0 ± 1.0	
Change from baseline	-8.5 ± 0.7	-5.6 ± 0.7	0.001
CGI-S score			
Baseline	4.7 ± 0.1	4.6 ± 0.1	
Endpoint	3.8 ± 0.3	4.1 ± 0.3	
Change from baseline	-1.0 ± 0.1	-0.6 ± 0.1	0.002
CGI-I Score			
Endpoint	2.7 ± 0.1	3.2 ± 0.1	
Range	1–5	1–6	<0.001
Responder, n (%)	51 (44)	28 (23)	0.002

CGI-I=Clinical Global Impressions – Improvement of Illness Scale; CGI-S=Clinical Global Impressions – Severity of Illness Scale; OCD=Obsessive Compulsive Disorder; Y-BOCS=Yale-Brown Obsessive-Compulsive Scale.

LUVOX® CR was statistically superior versus placebo in reducing the severity of illness, as measured by the CGI-S, and producing clinical improvement, as measured by the CGI-I. A CGI-I responder was defined as achieving a CGI-I rating of “very much improved” or “much improved.” The use of LUVOX® CR resulted in a significantly greater proportion of CGI-I responders, compared with placebo (44% versus 23%, p=0.002).

Safety Results: Of the 253 randomized patients, 84 (66%) in the LUVOX® CR group and 95 (75%) in the placebo group completed the study. A higher percentage of LUVOX® CR-treated patients (23 patients, 19%) discontinued due to AEs, compared to the placebo group (8 patients, 6%). For LUVOX® CR, the most common AE associated with discontinuation were nausea (7 patients, 6%), insomnia (6 patients, 5%), somnolence (5 patients, 4%), dizziness (4 patients, 3%), and diarrhea (3 patients, 2%). A total of 5 serious AEs were reported by 5 patients in the LUVOX® CR group, and 2 serious AEs were reported by 2 placebo group patients. All serious AEs were judged by the investigator to be either unlikely related or unrelated to study medication.

Most patients reported at least 1 treatment-emergent AE: 97% (n=120) of LUVOX® CR patients and 85% (n=106) of placebo patients. Treatment-emergent AEs reported by ≥10% of patients in either treatment group with a higher incidence (≥5% difference) in the LUVOX® CR group are shown in Table 39. Abnormal ejaculation and anorgasmia were reported by 4 (8%) and 6 (5%) patients treated with LUVOX® CR, respectively, and no patients in the placebo group. Impotence occurred with similar frequency in the LUVOX® CR (3 patients, 2%) and placebo (2 patients, 2%) groups. Decreased libido was reported by 9 patients (7%) in the LUVOX® CR group and 4 patients (3%) in the placebo group.

The mean change from baseline in body weight was between -0.8 kg and 0.1 kg in the LUVOX® CR group and between 0.0 kg and 0.5 kg in the placebo group.

TABLE 39. TREATMENT-EMERGENT ADVERSE EVENTS REPORTED BY ≥10% OF SUBJECTS AND WITH A DIFFERENCE IN INCIDENCE (≥5%) BETWEEN TREATMENT GROUPS

Adverse Event	LUVOX® CR (N=124) N (%)	Placebo (N=124) N (%)
Insomnia	43 (35)	25 (20)
Nausea	42 (34)	16 (13)
Somnolence	34 (27)	14 (11)
Asthenia	31 (25)	10 (8)
Infection	23 (19)	34 (27)
Diarrhea	22 (18)	10 (8)
Anorexia	16 (13)	6 (5)

Conclusion: The authors concluded that the study demonstrated that LUVOX® CR was significantly superior to placebo in all efficacy measures. They noted that the magnitude of decrease in the Y-BOCS and CGI-I scores achieved by patients treated with LUVOX® CR was similar to those observed in previous studies of fluvoxamine, fluoxetine, paroxetine, and sertraline. LUVOX® CR showed consistent earlier onset of therapeutic effects across different efficacy parameters compared with the results of previous studies involving other SSRIs. LUVOX® CR was safe and well tolerated at a dose of 100 to 300 mg/d over a period of 12 weeks, and treatment was not associated with weight gain. The percentage of patients discontinuing treatment with LUVOX® CR due to AEs was within the range of percentages reported for other SSRIs in OCD clinical studies.

CLINICAL EVIDENCE FOR LUVOX® CR IN SAD

Davidson J, Yaryura-Tobias J, DuPont R, et al. Fluvoxamine-controlled release formulation for the treatment of generalized social anxiety disorder. J Clin Psychopharmacol 2004;24(2):118-25.

Objectives: This multicenter, randomized, placebo-controlled, double-blind, parallel-group study was designed to compare the efficacy and safety of LUVOX® CR with that of placebo in patients with generalized social anxiety disorder (GSAD).

Subjects and Methods: Subjects included males and females aged 18–70 years who met DSM-IV criteria for GSAD according to the Modified Structured Clinical Interview for the DSM-IV, had a minimum score of 60 on the Liebowitz Social Anxiety Scale (LSAS) at screening, scored ≤18 on the Montgomery-Asberg Depression Rating Scale at screening, and were fluent in English. Patients were excluded from participation if they were pregnant, lactating, or using inadequate contraception; had a primary diagnosis of major depression, dysthymia, or panic disorder; had a history or current diagnosis of schizophrenia, psychosis, OCD, bipolar affective disorder, or borderline personality disorder; had evidence of substance or alcohol abuse in the past 6 months; had a positive urine drug screen; required CBT to treat SAD within the previous month; failed to discontinue psychotropic medication 14 days (30 for fluoxetine) prior to baseline; had a clinically significant medical condition; or required medications that could put them at risk for taking LUVOX® CR.

The mean age was 37 years for both groups, with a mean duration of GSAD of 21.9 and 22.2 years for LUVOX® CR and placebo, respectively. The sample was predominantly male (64%) and Caucasian (78.5%). Both groups had a low level of comorbid disease, with dysthymia as the most common comorbidity, occurring in 4% of LUVOX® CR and 3% of placebo patients.

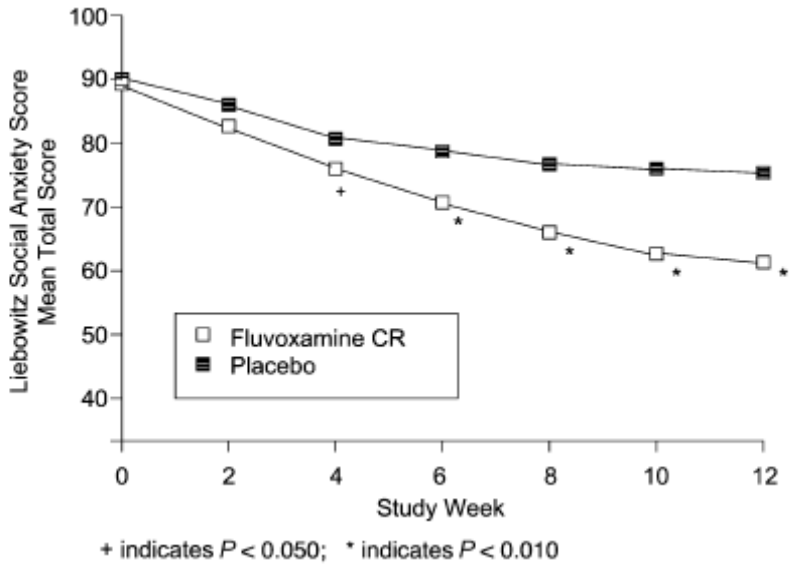
A total of 356 patients were screened, and 279 were randomized (LUVOX® CR=139, placebo=140). After a screening phase of 1 to 14 days, patients were randomized 1:1 to receive either LUVOX® CR or placebo for 12 weeks. LUVOX® CR was initiated at a dose of 100 mg/d, and the dose could be increased by 50 mg increments at 1-week intervals to a maximum dose of 300 mg/d. The dose remained constant during weeks 6 through 12. Patient visits occurred at screening, baseline, and weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12.

The primary outcome measure was change from baseline on the LSAS, and additional efficacy measures included the CGI-S, CGI-I, Sheehan Disability Scale (SDS), and the Patient Global Impression of Change (PGI). The CGI-I and PGI were not assessed at baseline. The ASEX assessed the effect of treatment on sexual function. The Montgomery-Asberg Depression Rating Scale was used to assess depression at the screening visit, and to evaluate the effect of LUVOX® CR treatment on any comorbid depressive symptoms at end point. Efficacy analyses were performed on the intent-to-treat population (LUVOX® CR=121, placebo=126), defined as all randomized patients who took at least 1 dose of study medication and who had at least 1 post-baseline efficacy measurement, using LOCF.

Results: Of the 279 randomized patients, 73 (53%) in the LUVOX® CR group and 87 (62%) in the placebo group completed the study. The reasons for withdrawal were similar between groups except for lack of efficacy (<1% of LUVOX® CR patients versus 8% of placebo patients) and adverse events (26% of LUVOX® CR group versus 1% of placebo group).

The mean change from baseline on the primary efficacy outcome (LSAS) was -26.7 (±2.6) for the LUVOX® CR group and -12.9 (±1.6) for the placebo group ($p<0.01$). These changes represent a 29.6% decrease from baseline on the LSAS total score for the LUVOX® CR group versus a 14.5% decrease for placebo patients. A statistically significant difference in LSAS scores in favor of LUVOX® CR was observed at week 4 and continued through week 12 (Figure 4). In addition, LUVOX® CR was also superior to placebo at week 4 through week 12 on the LSAS Fear subscale ($p<0.001$) and the LSAS Avoidance subscale ($p<0.001$).

FIGURE 4. LIEBOWITZ SOCIAL ANXIETY SCALE MEAN TOTAL SCORE BY VISIT



+ indicates $P < 0.050$; * indicates $P < 0.010$

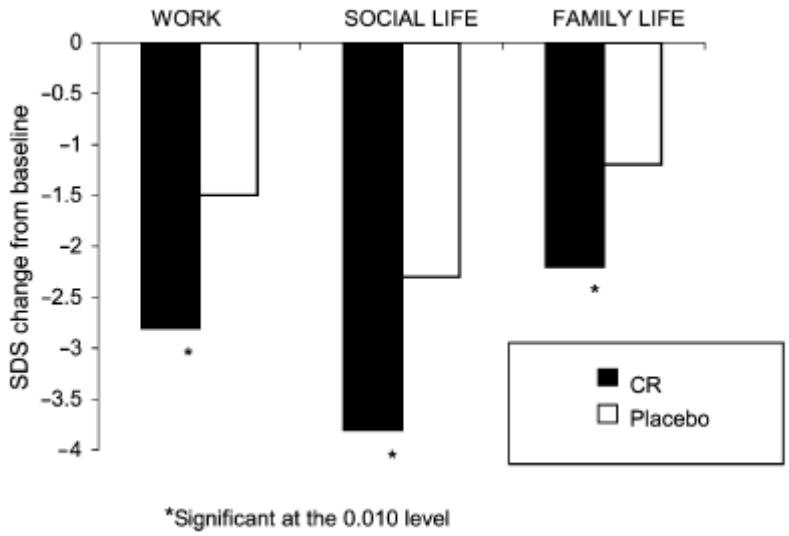
LUVOX® CR was also statistically superior to placebo on all secondary efficacy measures including the SDS, CGI-S, CGI-I, and the PGI (Table 40). A statistically significant difference was observed at week 4 and continued through week 12 on the CGI-I and at week 6 continuing through week 12 on the CGI-S, SDS, and the PGI. At study endpoint, the mean change from baseline in the SDS scores for the LUVOX® CR group was significantly reduced compared with placebo for all 3 items: work, social life, and family life/home responsibilities (Figure 5). The response rate based on the CGI-I scale, defined as a score of "very much improved" or "much improved" at endpoint, was 33.9% for the LUVOX® CR group and 16.7% for the placebo group (p<0.001). No statistically significant treatment difference was observed on the Montgomery-Asberg Depression Rating Scale at endpoint (p=0.308).

TABLE 40. SUMMARY OF SECONDARY EFFICACY VARIABLES AT BASELINE AND ENDPOINT

VARIABLE	LUVOX® CR (N=121)	PLACEBO (N=126)	P-VALUE
Sheehan Disability Scale Total Score			
Baseline mean (SE)	18.2 (0.49)	17.9 (0.45)	
Week 12 mean (SE)	12.1 (0.8)	14.4 (0.6)	0.017
CGI-S			
Baseline mean (SE)	4.6 (0.05)	4.6 (0.05)	
Week 12 mean (SE)	3.6 (0.1)	4.1 (0.1)	<0.001
CGI-I			
Week 2 mean (SE)	3.6 (0.1)	3.7 (0.1)	
Week 12 mean (SE)	2.8 (0.1)	3.4 (0.1)	<0.001
PGI			
Week 2 mean (SE)	3.6 (0.1)	3.5 (0.1)	
Week 12 mean (SE)	2.9 (0.1)	3.4 (0.1)	<0.001

CGI-I=Clinical Global Impressions – Improvement of Illness Scale; CGI-S=Clinical Global Impressions – Severity of Illness Scale; PGI=Patient Global Improvement Scale; SE=Standard Error.

FIGURE 5. SHEEHAN DISABILITY SCALE—MEAN CHANGE FROM BASELINE AT ENDPOINT



*Significant at the 0.010 level

The most frequently occurring treatment emergent adverse events in the LUVOX® CR group were headache (47 patients; 36%), nausea (40 patients; 31%), somnolence (40 patients; 31%), and insomnia (42 patients; 31%). The incidence of these adverse events was 27% (34 patients), 6% (7 patients), 10% (13 patients), and 11% (14 patients), respectively, in the placebo group. While the percentage of patients reporting these adverse events decreased over the course of the study, they still occurred more frequently in the drug than the placebo group (Table 41). The only severe event that occurred in ≥5% of patients was headache (8% [10 patients] in the LUVOX® CR group and 2% [2 patients] in the placebo group). Thirty-five (35) patients treated with LUVOX® CR were terminated from the study due to adverse events, for the following reasons: somnolence (12 patients; 9%), dizziness (9 patients; 7%), nausea (8 patients; 6%), insomnia (3 patients; 5%), and headache (3 patients; 5%). One placebo patient was discontinued from treatment due to nervousness. Most events leading to discontinuation from the study occurred early in treatment (in the first week) and were considered possibly or probably related to study medication.

TABLE 41. PREVALENCE OF TREATMENT-EMERGENT ADVERSE EVENTS

	WEEKS 0–2		WEEKS 6–8		WEEKS 10–12	
	LUVOX® CR %	PLACEBO %	LUVOX® CR %	PLACEBO %	LUVOX® CR %	PLACEBO %
Headache	25	22	14	2	13	1
Nausea	29	5	5	0	3	0
Somnolence	28	9	15	2	13	0
Insomnia	27	9	13	<1	6	1

There was no significant change in body weight, defined as 7% or more weight loss or gain, for either LUVOX® CR or placebo treatment groups during the 12-week treatment period (p>0.99). The mean weight at baseline was 79.2 kg (±1.5) and 79.1 kg (±1.6) for the LUVOX® CR and placebo groups, respectively. At week 12, the weight for the LUVOX® CR group was 78.9 kg (±0.0) and 78.5 kg (±0.2) for the placebo group.

Effects of treatment on sexual function were assessed by the ASEX scale and spontaneous adverse event reports. Statistically significant, but clinically small, differences between groups (favoring placebo and comparable to the endpoint values) occurred at each visit, but at endpoint, the change from baseline

was not statistically significantly different for patients treated with LUVOX® CR and placebo. The adverse event rates for abnormal ejaculation, decreased libido, anorgasmia, and impotence were 13% (10 male patients), 10% (13 male or female patients), 5% (6 male or female patients), and 1% (1 male patient), respectively, for LUVOX® CR-treated patients as compared with 1% (1 male patient), 6% (7 male or female patients), <1% (1 male or female patient), and 1% (1 male patient) for placebo-treated patients.

Conclusion: The authors concluded that the study showed that in GSAD, LUVOX® CR was superior to placebo on all efficacy measures, i.e., specific symptoms of fear and avoidance, global state, and impairment in work, family, and social functions. Efficacy began to emerge at week 4 on the primary efficacy and global measure and continued to increase relative to placebo at each time point thereafter. These positive results are consistent with the published studies of the SSRIs paroxetine and sertraline relative to placebo in GSAD, as well as the two reports of fluvoxamine maleate. A duration of treatment longer than 12 weeks may be necessary to achieve further reduction in GSAD symptoms, since LUVOX® CR-treated patients were still symptomatic at endpoint of the study. The side effect profile was characteristic of what is already known about fluvoxamine maleate in GSAD. As measured by the ASEX, there were clinically small, but statistically significant, differences between fluvoxamine CR and placebo throughout the trial, which had disappeared at endpoint. While LUVOX® CR was not associated with weight change in this 12-week study, its effect on weight needs to be studied in trials of longer duration.

Westenberg HG, Stein DJ, Yang H, Li D, Barbato LM. A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. J Clin Psychopharmacol 2004;24(1):49-55.

Objective: This multicenter, randomized, double-blind, placebo-controlled study was designed to compare the efficacy and safety of flexible dosing of LUVOX® CR (100–300 mg/d) to placebo during a 12-week treatment period in adult outpatients diagnosed with GSAD.

Subjects and Methods: Study participants were male and female outpatients aged 18 to 70 years with a predominant diagnosis of DSM-IV GSAD and a minimum score of 60 on the LSAS at screening. Subjects were excluded from the study who were pregnant, lactating, or using inadequate contraception; had a predominant diagnosis of major depression, dysthymia, or panic disorder in the past 6 months; had a history or current diagnosis of schizophrenia, psychosis, bipolar disorder, OCD, or borderline personality disorder; had a score of ≥18 on the Montgomery-Asberg Depression Rating Scale at screening; had evidence of a substance abuse or dependence disorder in the past 6 months; had a positive urine drug screen; were at serious risk for suicide; had an unstable or serious medical condition; required CBT to treat SAD in the past month; or did not discontinue psychotropic medications 14 days prior to baseline.

After a screening phase of 1–14 days, 300 patients were randomized to LUVOX® CR (n=149) or placebo (n=151) for 12 weeks. Subjects began LUVOX® CR at a dose of 100 mg/d at bedtime and were titrated up by 50-mg increments to a maximum dose of 300 mg/d over the first 5 weeks of treatment. The dose remained constant during weeks 6 through 12.

The mean age was 38.6 and 37.3 years, and mean duration of GSAD was 20.5 and 20.3 years for LUVOX® CR- and placebo-treated patients, respectively. About half of patients were male (46%). The baseline mean LSAS score was 94.8 for both groups, indicative of a severe level of impairment. The mean CGI-S was 4.8 and 4.7, defined as moderately ill to markedly ill, for the LUVOX® CR and placebo groups, respectively. The mean endpoint dose of LUVOX® CR was 209 mg, compared to an equivalent dose of 240 mg in the placebo group.

The primary outcome measure was change from baseline on the LSAS, and additional efficacy measures included the CGI-S, CGI-I, Sheehan Disability Scale (SDS), and the PGI. The CGI-I and PGI were not assessed at baseline. The ASEX assessed the effect of treatment on sexual function. The LSAS was administered at screening, baseline, and weeks 2, 4, 6, 8, 10, and 12. The CGI-S, SDS, and ASEX were administered at baseline, and weeks 2, 4, 6, 8, 10, and 12. The CGI-I and PGI were administered at weeks 2, 4, 6, 8, 10, and 12. Efficacy analyses were performed on the intent-to-treat population (LUVOX® CR=146, placebo=148), defined as all randomized patients who received at least 1 dose of study medication and who had a baseline assessment, and at least 1 post-baseline efficacy measurement, using LOCF and observed cases (OC) algorithms.

Results: Of the 300 randomized patients, 92 (62%) in the LUVOX® CR and 107 (71%) in the placebo group completed the study. The reasons for withdrawal were similar across treatment groups except for withdrawal due to lack of efficacy and withdrawal due to adverse experience. Fourteen patients (9%) in the placebo treatment group but no patients in the LUVOX® CR treatment group withdrew due to lack of efficacy. A higher percentage of patients in the LUVOX® CR treatment group (38 patients, 26%) than in the placebo treatment group (8 patients, 5%) discontinued due to adverse events. Of the LUVOX® CR patients who discontinued early from the study, most (20 patients) discontinued within the first 3 weeks of treatment.

Table 42 shows the change in primary and secondary efficacy parameters from baseline to endpoint. The mean reduction in LSAS score was 37% for LUVOX® CR and 28% for placebo patients (p=0.020). Subjects treated with LUVOX® CR experienced a significant reduction in LSAS beginning at 4 weeks (Figure 6).

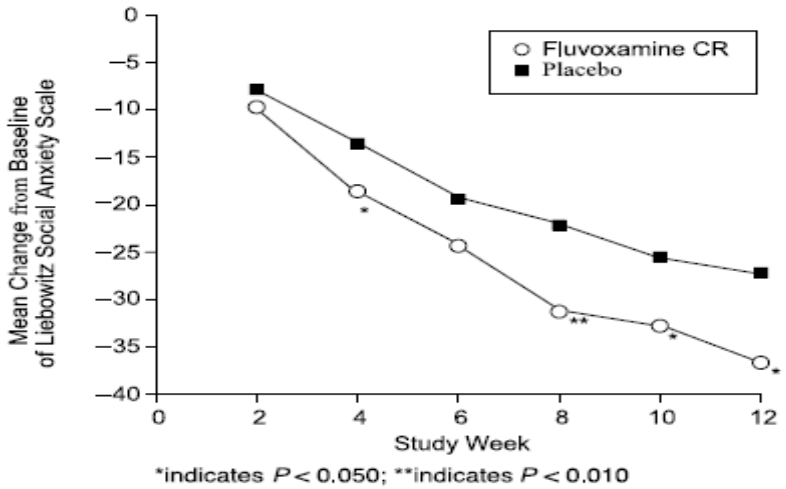
TABLE 42. EFFICACY PARAMETERS IN GSAD SUBJECTS (ITT POPULATION)

EFFICACY PARAMETER	LUVOX® CR (N=146)	PLACEBO (N=148)	P VALUE
LSAS Total Score			
Baseline	97.4	95.8	
Mean Change from Baseline (SE)	-36.1 (2.7)	-27.3 (2.4)	0.020
Sheehan Disability Scale			
Baseline	19.2	18.1	
Mean Change from Baseline (SE)	-7.8 (0.7)	-5.8 (0.6)	0.036
CGI-S			
Baseline	4.9	4.7	
Mean Change from Baseline (SE)	-1.5 (0.1)	-1.0 (0.1)	0.022
CGI-I			
Endpoint Score (SE)	2.5 (0.1)	2.9 (0.1)	0.026
Range	1–6	1–6	
Responders, N (%)	70 (48)	65 (44)	0.078
PGI			
Endpoint Score (SE)	2.6 (0.1)	3.0 (0.1)	0.051
Range	1–6	1–7	

CGI-I=Clinical Global Impressions – Improvement of Illness Scale ; CGI-S=Clinical Global Impressions – Severity of Illness Scale; LSAS=Liebowitz Social Anxiety Scale; PGI=Patient Global Improvement Scale; SE=Standard Error.

LUVOX® CR was also statistically superior to placebo in the secondary efficacy measures of CGI-S, SDS, and CGI-I at endpoint. The mean change from baseline to endpoint in SDS scores for the LUVOX® CR group was significantly reduced, compared with placebo, for the total score and the work item, but not for social and family life/home responsibilities (Figure 7). The treatment difference between LUVOX® CR and placebo was not statistically significant in mean change from baseline in the ASEX total score at endpoint, or at weeks 4, 6, 8, or 10 during the course of the study.

FIGURE 6. LIEBOWITZ SOCIAL ANXIETY SCALE—MEAN CHANGE FROM BASELINE BY STUDY VISIT



*indicates $P < 0.050$; **indicates $P < 0.010$

FIGURE 7. SHEEHAN DISABILITY SCALE—MEAN CHANGE FROM BASELINE TO ENDPOINT

Most patients in the Safety Population reported at least 1 treatment emergent sign and symptom during the study (LUVOX® CR 92%; placebo 83%). Most treatment emergent signs and symptoms were considered by the investigator to be mild or moderate in severity. The most frequently occurring adverse events in the LUVOX® CR treatment group were nausea (47%), headache (35%), insomnia (32%), asthenia (28%), and somnolence (22%). The incidence of these adverse events was 15%, 32%, 15%, 13%, and 7%, respectively, in the placebo treatment group. Most treatment emergent signs and symptoms leading to discontinuation were reported in the nervous system in both treatment groups (LUVOX® CR, 17%; placebo, 3%). The most common treatment emergent signs and symptoms leading to discontinuation in the LUVOX® CR treatment group were nausea (LUVOX® CR, 9%; placebo, 1%), insomnia (LUVOX® CR, 5%; placebo, 1%), and anxiety (LUVOX® CR, 5%; placebo, 1%). One serious adverse event was reported by a subject in the placebo treatment group. The adverse events related to sexual dysfunction reported in the LUVOX® CR treatment group were abnormal ejaculation (9%), anorgasmia (5%), impotence (1%), and libido decreased (7%). The incidence of these adverse events was 4%, 1%, 4%, and 4%, respectively, in the placebo group.

There was no significant difference between the LUVOX® CR and placebo groups with respect to markedly abnormal change in body weight, defined as a 7% or more weight gain or loss, during the study (p=0.999). The mean change from baseline to endpoint in the body weight was 0.1 ± 0.2 and 0.3 ± 0.2 for the LUVOX® CR and placebo groups, respectively (p=0.634).

Conclusion: The authors concluded that LUVOX® CR is an efficacious, safe, and well-tolerated treatment of GSAD, with low rates of sexual dysfunction or weight gain. During a 12-week treatment period, LUVOX® CR resulted in statistically superior outcomes relative to placebo on the primary efficacy variable (LSAS) and on 3 of 4 secondary efficacy variables (SDS, CGI-S, and CGI-I). The findings here that LUVOX® CR did not increase weight or cause sexual dysfunction may well promote adherence to medication.

Stein DJ, Westenberg HG, Yang H, Li D, Barbato LM. Fluvoxamine CR in the long-term treatment of social anxiety disorder: the 12- to 24-week extension phase of a multicentre, randomized, placebo-controlled trial. Int J Neuropsychopharmacol 2003; 6(4):317-23.

Objective: This was a double-blind, 12-week extension of a multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of flexible dosing of fluvoxamine CR (100 to 300 mg/d) to placebo during a 12-week treatment period in 300 adult outpatients with GSAD.

Subjects and Methods: Subjects (N=112) who had completed the acute phase study (Westenberg et al., 2004), and had shown at least minimal improvement (defined as a CGI-I score of 3 or less) were eligible to participate in this extension phase. Inclusion and exclusion criteria are described in Westenberg et al., 2004.

In the acute phase, dosage was titrated weekly during the first 5 weeks of the study, from 100 mg up to 300 mg at bedtime, in 50 mg increments, as tolerated. Subjects in the extension phase continued the endpoint dosage of fluvoxamine CR (n=57) or placebo (n=55) under double-blind conditions.

The primary efficacy variable was LSAS, and the CGI-I, CGI-S, and the SDS were secondary efficacy measures. In the extension phase, these measures were administered every 4 weeks (i.e., weeks 12, 16, 20, and 24), or on early termination. Statistical analyses were performed on the primary and secondary efficacy parameters for the intent-to-treat (ITT) population, using LOCF and observed cases.

Results: Of 112 patients who enrolled in the extension phase, 56 patients (98%) in the fluvoxamine CR treatment group and 53 patients (96%) in the placebo-treatment group were included in the ITT population (109 patients), and 47 (82%) in the LUVOX® CR and 43 (78%) in the placebo group completed the extension phase.

At baseline (day 1 of the acute phase), most demographic and clinical variables did not significantly differ between groups; however, placebo-treated patients had significantly lower CGI-S scores (p=0.043) and more Axis I disorders (p=0.05).

A decrease in LSAS total scores was seen in the LUVOX® CR group, compared with the placebo group, at week 12 in participants in the acute phase and at week 24 in participants in the extension phase (Figure 8). This difference in the LSAS was clearly significant at end of the acute phase, and despite the high dropout rate thereafter, analysis of data from baseline (day 1 of the acute phase) to endpoint demonstrated that the LSAS difference tended towards significance (p=0.074) (Table 43). Over the same time frame, severity of illness, as measured by the CGI-S, and disability, as measured by the SDS, were significantly lower in the LUVOX® CR group than in the placebo group (p=0.003 and p=0.028 respectively), with CGI-I differences in the same direction but not reaching statistical significance (Table 43).

FIGURE 8. MEAN CHANGE FROM BASELINE OF LIEBOWITZ SOCIAL ANXIETY SCALE (LSAS) IN THE ITT POPULATION (N=109) WITH LOCF IN EXTENSION PHASE (WEEKS 12–24)

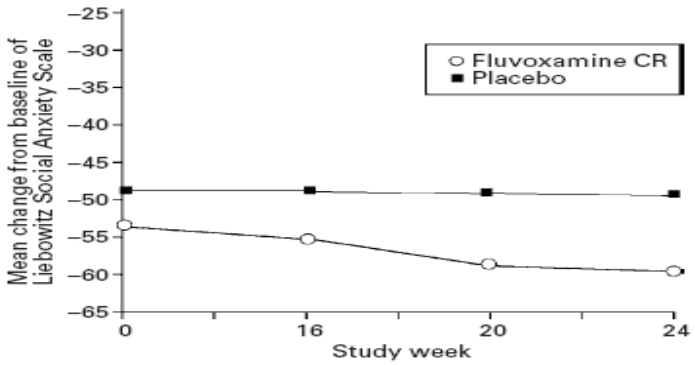


TABLE 43. MEAN CHANGE IN EFFICACY SCALES (ITT LOCF POPULATION)

Scale	Treatment Group	Mean Score on Day 1	Mean (SE) Change From Day 1 to Week 12	Mean (SE) Change From Day 1 to Week 24	Mean (SE) Change From Week 12 to Week 24 (endpoint)
LSAS	LUVOX® CR (n=56)	98.2	-53.2 (4.0)	-59.1 (4.0)	-6.3 (1.6)
	Placebo (n=53)	97.7	-47.9 (3.6)	-49.5 (3.8)	-1.6 (1.6)
	p value		0.260	0.074	0.109
CGI-S	LUVOX® CR (n=56)	5.0	-2.2 (0.2)	-2.6 (0.2)	-0.4 (0.1)
	Placebo (n=53)	4.7	-1.8 (0.2)	-1.9 (0.2)	-0.2 (0.1)
	p value		0.017*	0.003**	0.133
SDS	LUVOX® CR (n=55)	19.0	-11.5 (1.0)	-12.9 (1.0)	-1.5 (0.3)
	Placebo (n=52)	17.5	-9.4 (0.9)	-9.5 (1.0)	-0.1 (0.5)
	p value		0.150	0.028*	0.066

*Significant at the 0.050 level
**Significant at the 0.010 level
LSAS=Liebowitz Social Anxiety Scale; CGI-S=Clinical Global Impressions – Severity of Illness Scale; SDS=Sheehan Disability Scale; SE=Standard Error

Focusing on data from weeks 12 to 24 in those patients that remained in the study, it is apparent that further improvement occurred in the LUVOX® CR-treated patients compared to placebo-treated patients (Figure 8 and Table 43). Although the magnitude of changes was smaller in the extension phase than in the acute phase, the direction of the changes was the same. Similarly, the percentage of responders (defined as a score of 1 or 2 on the CGI-I, LOCF) was slightly higher in the LUVOX® CR group (80%) than in the placebo group (74%), although the difference was not significant (p=0.322). Again, the percentage of remitters (defined by a score of 1 on the CGI-I) was numerically higher in the LUVOX® CR group (38%) than in the placebo group (28%), but not significantly so (p=0.318).

Serious adverse events were reported by 2 patients in each treatment group, but none was considered related to study medication. Five patients (9%) in the LUVOX® CR group and 2 patients (4%) in the placebo group discontinued due to an adverse event. Most treatment-emergent signs and symptoms (TESS) were mild to moderate in severity, with no individual TESS evaluated as severe in more than 1 subject in the LUVOX® CR group or 2 patients in the placebo group. The overall incidence of TESS (i.e., patients who experienced at least one TESS) was higher in the LUVOX® CR group (39 patients, 68%) than in the placebo group (29 patients, 53%). TESS reported by ≥5% of the patients in either treatment group with a higher incidence (≥5% difference) in the LUVOX® CR group were limited to sweating (LUVOX® CR, 5 patients, 9%; placebo, 2 patients, 4%), nausea (LUVOX® CR, 4 patients, 7%; placebo, 1 subject, 2%), and abnormal ejaculation (LUVOX® CR, 4 patients, 7%; placebo, 0 patients).

The TESS profile was similar in the acute and extension phase in both the medication and placebo groups. TESS of special interest were reported for a higher percentage of patients in the LUVOX® CR group (12 patients, 21%) than in the placebo group (8 patients, 15%). Notably, TESS associated with sexual dysfunction were more common in the LUVOX® CR group (9 patients, 16%) than in the placebo group (3 patients, 5%). TESS reported by ≥5% of the patients in the LUVOX® CR group as study related included asthenia, headache, nausea, dry mouth, insomnia, sweating, and abnormal ejaculation.

No trends were observed suggesting a relationship between LUVOX® CR and serious abnormalities on vital signs, electrocardiograms, or laboratory investigations. In particular, there was no significant difference between LUVOX® CR and placebo groups with respect to markedly abnormal change in body weight, defined as 7% or more weight gain or loss, during the study. Indeed, further exploration of data on weight demonstrated that patients in the LUVOX® CR group weighed 74.7 (1.9) kg at day 1 and 75.4

(1.9) kg at week 24, while patients in the placebo group weighed 73.7 (2.2) kg at day 1 and 74.4 (2.2) kg at week 24 (LOCF), with no significant difference in weight change between the two groups (p=0.715).

Conclusion: The authors concluded that study results suggested that LUVOX® CR is an effective, safe, and well-tolerated treatment over the longer term in adults with SAD. During maintained treatment from weeks 12–24, patients on LUVOX® CR continued to improve, in contrast to patients on placebo. Although the magnitude of such changes are smaller than those seen in the acute phase, evidence that continued improvement is seen during longer term administration of medication supports the current expert consensus that treatment of SAD should continue beyond the acute phase.

LUVOX® CR FOR THE TREATMENT OF OCD AND SAD

LUVOX® CR is a once-daily therapy indicated as first-line treatment of OCD and SAD in adults, infrequently occurring but potentially debilitating conditions that are often under-recognized and under-treated. LUVOX® CR is not indicated for use in children or adolescents. LUVOX® CR uses SODAS® technology to deliver this formulation over 24 hours as a once-daily treatment.

OCD

OCD is a relatively rare, complex disorder that is associated with substantial disease burden. The long delays between onset of symptoms, correct diagnosis, and appropriate treatment adversely affect patients and their families and are associated with increased healthcare costs.

Fluvoxamine maleate has been long recognized as an effective and safe treatment for OCD. An optimal formulation of fluvoxamine was selected based on five Phase II studies involving more than 60 participants.[59]

- In clinical trials, compared to placebo:
  - LUVOX® CR demonstrates statistically significant reductions in OCD symptoms (as measured by the Y-BOCS) at week 12.
    - Statistical separation occurred as early as week 2.
    - Sustained improvement occurred through week 12.
  - LUVOX® CR is well tolerated.
  - Clinical evidence indicates that LUVOX® CR does not result in statistically significant weight gain or loss.

SAD

- SAD is a more common disorder that is associated with substantial patient distress and decrements in quality of life. Although those afflicted with SAD may frequently come into contact with PCPs, SAD remains under-detected; healthcare costs are substantially higher for patients with SAD than those without mental disorders.

- In clinical trials, compared to placebo:
  - LUVOX® CR is associated with significantly reduced SAD symptoms (as measured by the LSAS) at week 12.
    - Statistical separation occurred as early as week 4, although it was not sustained at week 6 in one study.
    - Sustained improvement occurred through week 12.

VALUE TO THE PAYER

LUVOX® CR is indicated for the treatment of OCD, a rare but severely disabling disorder, and SAD, a more common but also substantially impairing condition. Although both of these disorders have a profound effect on individuals' ability to function in occupational and social settings, they are frequently under-detected by patients' physicians or are inappropriately treated. These disorders place a high burden on patients' families, healthcare systems, and society in general.

Treatment for appropriately diagnosed patients with OCD or SAD includes psychotherapy and pharmacotherapy. For OCD, first-line, U.S. Food and Drug Administration (FDA)-approved pharmacological treatments include the SSRIs fluoxetine, fluvoxamine (IR and CR), paroxetine (IR and CR), and sertraline, and the SRI clomipramine. For SAD, first-line, FDA-approved pharmacological treatments include the SSRIs fluoxetine, fluvoxamine (CR), paroxetine (IR and CR), and sertraline, and the selective norepinephrine reuptake inhibitor (SNRI) venlafaxine (XR).

The recent addition of LUVOX® CR to the armamentarium of treatment options for OCD and SAD offers patients and physicians a once-daily medication with the ability to achieve clinically meaningful reductions in symptoms at 12 weeks and statistical separation from placebo as early as 2 and 4 weeks for OCD and SAD, respectively. In addition, LUVOX® CR is well tolerated, possesses a weight neutral profile (no significant weight gain or loss), and has a low incidence of sexual side effects. The drug delivery technology utilized by LUVOX® CR, SODAS® (Spheroidal Oral Drug Absorption System), is specifically formulated to deliver:

- Less peak and trough fluctuation in plasma levels compared to the IR formulation
- Lower and later peak plasma concentrations of fluvoxamine
- Higher trough concentrations of fluvoxamine

Reduced fluctuations in plasma concentration may be associated with a lower incidence of peak-related adverse events; a lower peak concentration may allow patients to initiate treatment at a higher dose without increasing the risk of peak-related adverse events.

In sum, patients with OCD and SAD often suffer silently with devastating symptoms for many years before receiving help. Because there are now a number of effective pharmacological treatments for these disorders, physicians may work with patients to determine the medication that best suits the needs of the individual, and take into consideration issues of time to effect, tolerability, and convenience. LUVOX® CR should be considered, along with other FDA-approved treatments, for these conditions.

CLINICAL SUMMARY SPREADSHEET

Key: AE=Adverse event; ASEX=Arizona Sexual Experiences Scale; BL=Baseline; CGI-I=Clinical Global Impressions – Improvement Scale; CGI-S=Clinical Global Impressions – Severity Scale; d=day; DB=Double blind; D/C=discontinue; Dx=diagnosis; ECT=electroconvulsive therapy; endpt=Endpoint; HAM-D=Hamilton Rating of Depression Scale; Hx=history; ITT=Intent to treat; LOCF=Last observation carried forward; LSAS=Liebowitz Social Anxiety Scale; LUV-CR=LUVOX® CR; MADRAS=Montgomery-Asberg Depression Rating Scale; mo=month; NS=Not significant; Outpt=outpatient; PC=Placebo-controlled; PG=Parallel group; PGI=Patient Global Improvement Scale; PLA=Placebo; Pt=Patient; RAN=Randomized; SDS=Sheehan Disability Scale; Sig=Significant; Sxs=Symptoms; Tx=Treatment; vs=versus; wk=week; Y-BOCS=Yale-Brown Obsessive-Compulsive Scale; yrs=Years

Citation	Design/ Duration	Treatments	Inclusion & Exclusion Criteria / Sample Size	Endpoints	Results	Conclusion
LUVOX® CR in OCD						
Hollander E, Koran LM, Goodman WK, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive compulsive disorder. J Clin Psychiatry 2003; 64(6):640-7.	12-wk RAN DB PC PG	After 1-wk PLA washout: LUV-CR titrated to effect over first 6 wks (100–300 mg/d) then constant dose over second 6 wks. PLA	Inclusion: outpts age ≥18 yrs; met DSM-IV criteria for OCD; Y-BOCS ≥21; HAM-D ≤16. Exclusion: other current primary DSM-IV dx; sig risk of suicide; + urine drug screen; pregnant, lactating, inadequate contraception; ECT w/I past 90 d; non-response to adequate trial of SRI for OCD; concomitant use of psychotropic or psychotherapeutic drugs astemizole, cisapride, terfenadine, theophylline, warfarin, digoxin, diltiazem, propranolol, OTC herbals or weight loss agents w/psychotropic properties. RAN N=253 ITT N=237	ITT LOCF Analysis Primary: Mean change from BL to endpt in Y-BOCS. Secondary: Mean change from BL to endpt in CGI-S, mean CGI-I @ endpt. % responders (CGI-I "very much improved" or "very improved" @ endpt). % pts w/ Y-BOCS reduction ≥25% and ≥35%. % remitted pts (Y-BOCS ≤8 @ endpt). % remitted pts (Y-BOCS ≤16 @ endpt).	Primary: Mean Δ Y-BOCS from BL: LUV-CR: -8.5 (0.7) 31.7% change PLA: -5.6 (0.7) 21.2% change LUV-CR vs PLA (p=001) Secondary: Mean Δ CGI-S from BL: LUV-CR: -1.0 (0.1) PLA: -0.6 (0.1) P=0.002 Mean CGI-I @ endpt: LUV-CR: 2.7 (0.1) PLA: 3.2 (0.1) p<0.001 % responders: LUV-CR: 44% PLA: 23% P=0.002 % Y-BOCS ≥25%: LUV-CR: 63% PLA: 46% P=0.009 % Y-BOCS ≥35%: LUV-CR: 45% PLA: 30% P=0.016 % remitted (Y-BOCS ≤8): LUV-CR: 18%	LUV-CR superior to PLA on all efficacy measures. Magnitude of decrease on Y-BOCS with LUV-CR similar to that seen in fluvoxamine, fluoxetine, paroxetine, sertraline. Consistent earlier onset of therapeutic effect compared with results of previous studies with other SSRIs.

Citation	Design/ Duration	Treatments	Inclusion & Exclusion Criteria / Sample Size	Endpoints	Results	Conclusion
					PLA: 8% P=0.019 % remitted (Y-BOCS ≤16): LUV-CR: 44% PLA: 31% P=0.045 Safety: % pts tx-emergent AE: LUV-CR: 97% PLA: 85% % D/C'd due to AE: LUV-CR: 19% PLA: 6% Sexual AE: Abnormal ejaculation & anorgasmia: LUV-CR:8% PLA: 5% Impotence: LUV-CR: 2% PLA: 2% Decreased libido: LUV-CR: 7% PLA: 3% Mean weight Δ: LUV-CR: -0.8 kg PLA: 0 kg	

Citation	Design/ Duration	Treatments	Inclusion & Exclusion Criteria / Sample Size	Endpoints	Results	Conclusion
LUVOX® CR in SAD						
Davidson J, Yaryura-Tobias J, DuPont R, et al. Fluvoxamine-controlled release formulation for the treatment of generalized social anxiety disorder. J Clin Psychopharmacol 2004;24(2):118-25.	12-wk RAN DB PC PG	LUV-CR titrated to effect over first 6 wks (100-300 mg/d) then constant dose over second 6 wks. PLA	Inclusion: male or female age 18-70 yrs; DSM-IV dx of GSAD; LSAS ≥60; MADRAS ≤18; fluent in English. Exclusion: pregnant or lactating women; inadequate use of contraceptives in premenopausal women; primary comorbid MDD, dysthymia, panic disorder; hx or current dx of schizophrenia, psychosis, OCD, bipolar disorder, borderline personality disorder; alcohol/drug abuse w/I past 6 mo; + urine drug screen; require CBT w/I past mo to treat SAD; failure to d/c psychotropic meds w/I 14 d (fluoxetine 30 d) of BL; clinically sig medical condition; required meds that placed them at risk for taking LUV-CR. RAN N=279 ITT N=247	Primary: Mean Δ from BL to endpt on LSAS Secondary: Mean Δ from BL to endpt on CGI-S, SDS, ASEX; mean CGI-I and PGI @ endpt. % responders (CGI-I "very much improved" or "very improved" @ endpt).	Primary: Mean Δ from BL to endpt on LSAS: LUV-CR: -26.7 (2.6) 29.6% decrease PLA: -12.9 (1.6) 14.5% decrease LUV-CR vs PLA, p<0.01 Secondary: Mean Δ from BL to endpt on CGI-S: BL: LUV-CR: 4.6 (0.05) PLA: 4.6 (0.05) Endpoint: LUV-CR: 3.6 (0.1) PLA: 4.1 (0.1) LUV-CR vs PLA, p<0.001 Mean Δ from BL to endpt on SDS: BL: LUV-CR: 18.2 (0.49) PLA: 17.9 (0.45) Endpoint: LUV-CR: 12.1 (0.8) PLA: 14.4 (0.6) LUV-CR vs PLA, p=0.017 Mean Δ from Wk 2 to endpt on CGI-I: Week 2: LUV-CR: 3.6 (0.1) PLA: 3.7 (0.1) Endpoint: LUV-CR: 2.8	LUV-CR was superior to PLA on all efficacy measures. Efficacy began to emerge at week 4 and continued to increase at each time point versus placebo. Results were similar to other trials of SSRIs in GSAD. Study sample had severe SAD and functional impairment and may have been more resistant to tx than other study samples. Safety profile was consistent with known AE associated with drug.

Citation	Design/ Duration	Treatments	Inclusion & Exclusion Criteria / Sample Size	Endpoints	Results	Conclusion
					(0.1) PLA: 3.4 (0.1) LUV-CR vs PLA, p<0.001 Mean Δ from Wk 2 to endpt on PGI: Week 2: LUV-CR: 3.6 (0.1) PLA: 3.5 (0.1) Endpoint: LUV-CR: 2.8 (0.1) PLA: 3.4 (0.1) LUV-CR vs PLA, p<0.001 % responders: LUV-CR: 33.9% PLA: 16.7% p<0.001 Safety: Most common AE: Headache: LUV-CR: 36% PLA: 27% Nausea: LUV-CR: 31% PLA: 6% Somnolence: LUV-CR: 31% PLA: 10% Insomnia: LUV-CR: 31% PLA: 11% % of AE decreased during course of study % D/C'd due to AE: LUV-CR: 26% PLA: 1% % D/C'd due to lack of efficacy: LUV-CR:<1%	

Citation	Design/ Duration	Treatments	Inclusion & Exclusion Criteria / Sample Size	Endpoints	Results	Conclusion
					PLA: 8% No sig change in body weight, ASEX Sexual AE: Abnormal ejaculation: LUV-CR: 13% PLA 1% Impotence: LUV-CR: 1% PLA 1% Decreased libido: LUV-CR: 10% PLA: 6% Anorgasmia: LUV-CR: 5% PLA: <1%	

Citation	Design/ Duration	Treatments	Inclusion & Exclusion Criteria / Sample Size	Endpoints	Results	Conclusion
Westenberg HG, Stein DJ, Yang H, Li D, Barbato LM. A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. J Clin Psychopharmacol 2004;24(1):49-55.	12-wk RAN DB PC PG	LUV-CR titrated to effect over first 5 wks (100–300 mg/d) then constant dose over second 7 wks. PLA	Inclusion: male and female outpatients aged 18 to 70 years with a predominant diagnosis of DSM-IV GSAD and a minimum score of 60 on the LSAS at screening. Exclusion: pregnant, lactating, or using inadequate contraception; a predominant diagnosis of major depression, dysthymia, or panic disorder in the past 6 mos; hx or current dx of schizophrenia, psychosis, bipolar disorder, OCD, or borderline personality disorder; score of ≥18 on the MADRAS at screening; evidence of a substance abuse or dependence disorder in the past 6 mos; positive urine drug screen; at serious risk for suicide; unstable or serious medical condition; required CBT to treat SAD in the past mo; or did not discontinue psychotropic medications 14 d prior to BL.	Primary: Mean Δ from BL to endpt on LSAS Secondary: Mean Δ from BL to endpt on CGI-S, SDS, ASEX; mean CGI-I and PGI @ endpt. % responders (CGI-I "very much improved" or "very improved" @ endpt).	Primary: Mean Δ from BL to endpt on LSAS: LUV-CR: -36.1 (2.7) 37% decrease PLA: -27.3 (2.4) 28% decrease LUV-CR vs PLA, p=0.020. Secondary: Mean Δ from BL to endpt on CGI-S: BL: LUV-CR: -1.5 (0.1) PLA: -1.0 (0.1) LUV-CR vs PLA, p=0.022 Mean Δ from BL to endpt on SDS: BL: LUV-CR: -7.8 (0.7) PLA: -5.8 (0.6) LUV-CR vs PLA, p=0.036 Mean CGI-I @ endpt: LUV-CR: 2.5 (0.1) PLA: 2.9 (0.1) LUV-CR vs PLA, p=0.026 % CGI-I responders: LUV-CR: 48% PLA: 44% P=0.078 Mean CGI-I @ endpt: LUV-CR: 2.6 (0.1) PLA: 3.0 (0.1) LUV-CR vs PLA, p=0.051	The authors concluded that LUVOX® CR is an efficacious, safe, and well-tolerated treatment of GSAD, with low rates of sexual dysfunction or weight gain.

Citation	Design/ Duration	Treatments	Inclusion & Exclusion Criteria / Sample Size	Endpoints	Results	Conclusion
Stein DJ, Westenberg HG, Yang H, Li D, Barbato LM. Fluvoxamine CR in the long-term treatment of social anxiety disorder: the 12- to 24-week extension phase of a multicentre, randomized, placebo-controlled trial. Int J Neuropsychopharmacol 2003; 6(4):317-23.	12-wk DB extension study for pts completing 12-wk RAN DB PC acute-phase study	In the acute phase, patients were titrated to LUV-CR 100-300 mg/d or PLA over 12 weeks. In the extension phase, patients rec'd the endpt dosage of LUV-CR or PLA under DB conditions.	Subjects who had completed the acute phase study (Westenberg et al., 2004), and had shown at least minimal improvement [defined as a CGI-I score of 3 or less] were eligible. N=112	Primary: Mean Δ LSAS Secondary: Mean Δ on CGI-S, SDS; & mean CGI-I @ wk 24. % responders (CGI-I "very much improved" or "very improved" @ endpt). % remitted (CGI-I "very much improved" @ endpt.	Mean Δ LSAS: Day 1 to wk 12: LUV-CR: -53.2 (0.4) PLA: -47.9 (3.6) NS Day 1 to wk 24: LUV-CR: -59.1 (0.4) PLA: -49.5 (3.8) NS Wk 12 to wk 24: LUV-CR: -6.3 (1.6) PLA: -1.6 (1.6) NS Mean Δ CGI-S: Day 1 to wk 12: LUV-CR: -2.2 (0.2) PLA: -1.8 (0.2) P=0.017 Day 1 to wk 24: LUV-CR: -2.6 (0.2) PLA: -1.9 (0.2) P=0.003 Wk 12 to wk 24: LUV-CR: -0.4 (0.1) PLA: -0.2 (0.1) NS Mean Δ SDS: Day 1 to wk 12: LUV-CR: -11.5 (1.0) PLA: -9.4 (0.9) NS Day 1 to wk 24: LUV-CR:	Subjects continued to improve while maintained on LUV-CR during wks 12-24. Although the magnitude of change was smaller than seen in the first 12 weeks of tx, continued improvement suggests that patients should be treated for SAD beyond the first 12 wks.

Citation	Design/ Duration	Treatments	Inclusion & Exclusion Criteria / Sample Size	Endpoints	Results	Conclusion
					-12.9 (1.0) PLA: -9.5 (1.0) P=0.028 Wk 12 to wk 24: LUV-CR: -1.5 (0.3) PLA: -0.1 (0.5) P=0.066 % CGI-I responders wk 24: LUV-CR: 80% PLA: 74% NS % CGI-I remitters wk 24: LUV-CR: 38% PLA: 28% NS Safety: % D/C'd due to AE: LUV-CR: 9% PLA: 4% Most AE mild or moderate. Higher incidence of sweating, nausea and abnormal ejaculation in LUV-CR vs PLA Incidence of tx-emergent AE: LUV-CR: 68% PLA: 53% % reporting sexual dysfunction AEs: LUV-CR: 16% PLA: 5% No sig change in body weight, vital signs, ECG, lab tests	

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